# Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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## Guidelines Development Process

### Table 1. Outline of the Guidelines Development Process

| Topic | Comment |
|---|---|
| **Goal of the guidelines** | Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents (ARVs) for the treatment of HIV infection in adults and adolescents in the United States. |
| **Panel members** | The Panel is composed of approximately 45 voting members who have expertise in HIV care and research, and includes at least one representative from each of the following U.S. Department of Health and Human Services (HHS) agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource and Services Administration (HRSA), and National Institutes of Health (NIH). Approximately two-thirds of the Panel members are non-governmental scientific members. The Panel also includes four to five community members with knowledge in HIV treatment and care. The U.S. government representatives are appointed by their respective agencies; other Panel members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4 year term with an option for reappointment for an additional term. See the Panel Roster for a list of current Panel members. |
| **Financial disclosure** | All members of the Panel submit a written financial disclosure annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* website (http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf). |
| **Users of the guidelines** | HIV treatment providers |
| **Developer** | Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC) |
| **Funding source** | Office of AIDS Research, NIH |
| **Evidence collection** | The recommendations in the guidelines are based on studies published in peer reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines. |
| **Recommendation grading** | As described in Table 2 |
| **Method of synthesizing data** | Each section of the guidelines is assigned to a working group of Panel members with expertise in the section's area of interest. The working groups synthesize available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Recommendations endorsed by the Panel are included in the guidelines. |
| **Other guidelines** | These guidelines focus on ART use for HIV-infected adults and adolescents. For more detailed discussion on the use of antiretroviral therapy (ART) for children and pre-pubertal adolescents (SMR Stages I – III), clinicians should refer to the Pediatric Antiretroviral Guidelines.<br><br>These guidelines also include a brief discussion on the management of women of reproductive age and pregnant women. |
| **Update plan** | The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety or efficacy data, or other information that may have an impact on the clinical care of patients. In the event of new data of clinical importance, the Panel may post an interim announcement with recommendations on the AIDS*info* website until the guidelines can be updated with the appropriate changes. Updated guidelines are available on the AIDS*info* website (http://www.aidsinfo.nih.gov). |
| **Public comments** | A 2-week public comment period follows release of the updated guidelines on the AIDS*info* website. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov. |



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**Table 2. Rating Scheme for Recommendations**

| Strength of Recommendation | Quality of Evidence for Recommendation |
|---|---|
| **A:** Strong recommendation for the statement<br>**B:** Moderate recommendation for the statement<br>**C:** Optional recommendation for the statement | **I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints<br>**II:** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes<br>**III:** Expert opinion |



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**Table 3. Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a]** (page 1 of 2)

| Laboratory Test | Timepoint/Frequency of Testing | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Entry into Care | ART Initiation[b] or Modification | 2 to 8 Weeks After ART Initiation or Modification | Every 3 to 6 Months | Every 6 Months | Every 12 Months | Treatment Failure | Clinically Indicated | If ART Initiation is Delayed[c] |
| **HIV Serology** | √<br>If HIV diagnosis has not been confirmed | | | | | | | | |
| **CD4 Count** | √ | √ | | √<br>During first 2 years of ART or if viremia develops while patient on ART or CD4 count <300 cells/mm$^3$ | | √<br>After 2 years on ART with Consistently Suppressed Viral Load:<br>*CD4 Count 300–500 cells/mm$^3$:*<br>• Every 12 months<br>*CD4 Count >500 cells/mm$^3$:*<br>• CD4 monitoring is optional | √ | √ | √<br>Every 3-6 months |
| **HIV Viral Load** | √ | √ | √[d] | √[e] | √[e] | | √ | √ | Repeat testing is optional |
| **Resistance Testing** | √ | √[f] | | | | | √ | √ | √[f] |
| **HLA-B*5701 Testing** | | √<br>If considering ABC | | | | | | | |
| **Tropism Testing** | | √<br>If considering a CCR5 antagonist | | | | | √<br>If considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen | √ | |



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**Table 3. Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a]** (page 2 of 2)

| Laboratory Test | Timepoint/Frequency of Testing | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Entry into Care | ART Initiation[b] or Modification | 2 to 8 Weeks After ART Initiation or Modification | Every 3 to 6 Months | Every 6 Months | Every 12 Months | Treatment Failure | Clinically Indicated | If ART Initiation is Delayed[c] |
| **Hepatitis B Serology[g,h]** | √ | √<br>May repeat if patient is nonimmune and not chronically infected with HBV[h] | | | | √<br>May repeat if patient is nonimmune and not chronically infected with HBV[h] | | √ | |
| **Hepatitis C Antibody Test**<br>(if positive, confirm with HCV RNA test) | √ | √<br>May repeat for at-risk patients if negative result at baseline | | | | √<br>May repeat for at-risk patients if negative result at baseline | | √ | |
| **Basic Chemistry[i,j]** | √ | √ | √ | √ | | | | √ | √<br>Every 6-12 months |
| **ALT, AST, T. bilirubin** | √ | √ | √ | √ | | | | √ | √<br>Every 6-12 months |
| **CBC with Differential** | √ | √ | √<br>If on ZDV | √<br>If on ZDV or if CD4 testing is done | √ | | | √ | √<br>Every 3-6 months |
| **Fasting Lipid Profile[k]** | √ | √ | | | √<br>If abnormal at last measurement | √<br>If normal at last measurement | | √ | √<br>If normal at baseline, annually |
| **Fasting Glucose or Hemoglobin A1C** | √ | √ | | √<br>If abnormal at last measurement | | √<br>If normal at last measurement | | √ | √<br>If normal at baseline, annually |
| **Urinalysis[j,l]** | √ | √ | | | √<br>If on TAF or TDF[l] | √ | | √ | |
| **Pregnancy Test** | | √<br>In women with child-bearing potential | | | | | | √ | |


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[a] This table pertains to laboratory tests done to select an ARV regimen and monitor for treatment responses or ART toxicities. Please refer to the HIV Primary Care guidelines for guidance on other laboratory tests generally recommended for primary health care maintenance of HIV patients.[1]

[b] If ART initiation occurs soon after HIV diagnosis and entry into care, repeat baseline laboratory testing is not necessary.

[c] ART is indicated for all HIV-infected individuals and should be started as soon as possible. However, if ART initiation is delayed, patients should be retained in care, with periodic monitoring as noted above.

[d] If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until viral load is suppressed to <200 copies/mL, and thereafter, every 3 to 6 months.

[e] In patients on ART, viral load typically is measured every 3 to 4 months. However, for adherent patients with consistently suppressed viral load and stable immunologic status for more than 2 years, monitoring can be extended to 6-month intervals.

[f] Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should also test for resistance mutations to this class of drugs. In ART-naive patients who do not immediately begin ART, repeat testing before initiation of ART is optional if resistance testing was performed at entry into care. In virologically suppressed patients who are switching therapy because of toxicity or for convenience, viral amplification will not be possible; therefore, resistance testing should not be performed. Results from prior resistance testing can be helpful in constructing a new regimen.

[g] If HBsAg is positive, TDF or TAF plus either FTC or 3TC should be used as part of the ARV regimen to treat both HBV and HIV infections. Preliminary data from clinical trials have demonstrated TAF activity against HBV. Final results from ongoing clinical trials will help to define the role of TAF in the treatment of HBV/HIV coinfection.

[h] If HBsAg, HBsAb, and anti-HBc are negative, hepatitis B vaccine series should be administered. Refer to HIV Primary Care and Opportunistic Infections guidelines for more detailed recommendations.[1,2]

[i] Serum Na, K, $HCO_3$, Cl, BUN, creatinine, glucose (preferably fasting), and creatinine-based estimated glomerular filtration rate. Serum phosphorus should be monitored in patients with chronic kidney disease who are on TAF- or TDF-containing regimens.[3]

[j] Consult the Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America for recommendations on managing patients with renal disease.[3] More frequent monitoring may be indicated for patients with evidence of kidney disease (e.g., proteinuria, decreased glomerular filtration) or increased risk of renal insufficiency (e.g., patients with diabetes, hypertension).

[k] Consult the National Lipid Association's recommendations for management of patients with dyslipidemia.[4]

[l] Urine glucose and protein should be assessed before initiating TAF- or TDF- containing regimens, and monitored during treatment with these regimens.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; Cl = chloride; CrCl = creatinine clearance; EFV = efavirenz; FTC = emtricitabine; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; $HCO_3$ = bicarbonate; K = potassium; NA = sodium; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine



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**Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring[a]**

| Clinical Scenario | Viral Load Monitoring | CD4 Count Monitoring |
|---|---|---|
| Before initiating ART | At entry into care **(AIII)**<br>If ART initiation is deferred, repeat before initiating ART **(AIII)**.<br>In patients not initiating ART, repeat testing is optional **(CIII)**. | At entry into care **(AI)**<br>If ART is deferred, every 3 to 6 months **(AIII)**.[b] |
| After initiating ART | Preferably within 2 to 4 weeks (and no later than 8 weeks) after initiation of ART **(AIII)**; thereafter, every 4 to 8 weeks until viral load suppressed **(BIII)**. | 3 months after initiation of ART **(AIII)** |
| After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression | 4 to 8 weeks after modification of ART to confirm effectiveness of new regimen **(AIII)**. | Monitor according to prior CD4 count and duration on ART, as outlined below. |
| After modifying ART because of virologic failure | Preferably within 2 to 4 weeks (and no later than 8 weeks) after modification **(AIII)**; thereafter, every 4 to 8 weeks until viral load suppressed **(BIII)**. If viral suppression is not possible, repeat viral load every 3 months or more frequently if indicated **(AIII)**. | Every 3 to 6 months **(AI)** |
| During the first 2 years of ART | Every 3 to 4 months **(AIII)** | Every 3 to 6 months[a] **(BII)** |
| After 2 years of ART (VL consistently suppressed, CD4 consistently 300-500 cells/mm$^3$) | Can extend to every 6 months for patients with consistent viral suppression for ≥2 years **(AIII)**. | Every 12 months **(BII)** |
| After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm$^3$) | | Optional **(CIII)** |
| While on ART with detectable viremia (VL repeatedly >200 copies/mL) | Every 3 months **(AIII)** or more frequently if clinically indicated. (See Virologic Failure and Suboptimal Immunologic Response section) | Every 3 to 6 months **(AIII)** |
| Change in clinical status (e.g., new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or antineoplastic therapy) | Every 3 months **(AIII)** | Perform CD4 count and repeat as clinically indicated[c] **(AIII)** |

[a] Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, adds to costs, and is not routinely recommended **(BIII)**.

[b] Some experts may repeat CD4 count every 3 months in patients with low baseline CD4 count (<200–300 cells/mm$^3$) before ART but every 6 months in those who initiated ART at higher CD4 cell count (e.g., >300 cells/mm$^3$).

[c] The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infections (OI), such as new HIV-associated symptoms, or initiation of treatment with medications which are known to reduce CD4 cell count.



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**Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)**

| Clinical Setting/Recommendation | Rationale |
|---|---|
| **Drug-resistance assay recommended** | |
| **In acute (early) HIV infection:** Drug-resistance testing is recommended **(AII)**. A genotypic assay is generally preferred **(AIII)**.<br>Treatment should not be delayed while awaiting results of resistance testing **(AIII)**.<br><br>If ART is deferred, repeat resistance testing may be considered when therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**. | Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified once resistance test results are available. Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.<br><br>Repeat testing when ART is initiated may be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection). |
| **In ART-naive patients with chronic HIV infection:** Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART **(AII)**. A genotypic assay is generally preferred **(AIII)**.<br><br>If an INSTI is considered for an ART-naive patient **and** transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay **(BIII)**.<br><br>If therapy is deferred, repeat resistance testing may be considered before initiation of ART (CIII). A genotypic assay is generally preferred **(AIII)**.<br><br>If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays). | Transmitted HIV with baseline resistance to at least 1 drug is seen in 10% to 17% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated, chronically infected patients.<br><br>Genotypic assays provide information on resistance to NRTIs, NNRTIs, PIs, and INSTIs. In some circumstances, INSTI-resistance tests need to be ordered separately (clinicians should check with the testing laboratory).<br><br>Currently, transmitted INSTI resistance is infrequent, but the risk of a patient acquiring INSTI-resistant strains may be greater in certain known exposure settings.<br><br>Repeat testing before initiation of ART may be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection).<br><br>Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus. |
| **In patients with virologic failure:** Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL **(AI)**. In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may not be successful but should still be considered **(BII)**.<br><br>A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens **(AII)**.<br><br>When virologic failure occurs while a patient is on an INSTI-based regimen, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens **(AII)**.<br><br>If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-receptor Tropism Assays).<br><br>Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**. | Drug-resistance testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen.<br><br>Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy.<br><br>Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant HIV.<br><br>Genotypic assays provide information on resistance to NRTI-, NNRTI-, PI-, and INSTI-associated mutations. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory).<br><br>Phenotypic testing can provide additional useful information in patients with complex drug resistance mutation patterns, particularly to PIs. |



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**Table 5. Recommendations for Using Drug-Resistance Assays (page 2 of 2)**

| Clinical Setting/Recommendation | Rationale |
|---|---|
| **In patients with suboptimal suppression of viral load:** Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART **(AII)**. | Testing can determine the role of resistance and thus help the clinician identify the number of active drugs available for a new regimen. |
| **In HIV-infected pregnant women:** Genotypic resistance testing is recommended for all pregnant women before initiation of ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. | The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient. However, treatment should not be delayed while awaiting results of resistance testing. The initial regimen can be modified once resistance test results are available. |
| **Drug-resistance assay not usually recommended** | |
| **After therapy is discontinued:** Drug-resistance testing is not usually recommended more than 4 weeks after ARV drugs are discontinued **(BIII)**. | Drug-resistance mutations may become minor species in the absence of selective drug pressure, and available assays may not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species. |
| **In patients with low HIV RNA levels:** Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL **(AIII)**. | Resistance assays cannot be consistently performed given low HIV RNA levels. |

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor



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**Table 6. Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-Naive Patients**

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, and resistance test results. Some regimens listed in this table may not be appropriate for patients with renal impairment. See Appendix B, Table 7, and the product prescribing information for recommendations on ARV dose modification in the setting of renal impairment. Drug classes and regimens within each class are arranged first by evidence rating and when ratings are equal, in alphabetical order.

| **Recommended Regimen Options**<br>Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. |
|---|
| INSTI plus 2-NRTI Regimen:<br>• DTG/ABC/3TC[a] **(AI)—if HLA-B*5701 negative**<br>• DTG plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)**<br>• EVG/c/TAF/FTC **(AI)** or EVG/c/TDF/FTC **(AI)**<br>• RAL plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)**<br><br>Boosted PI plus 2 NRTIs:<br>• DRV/r plus either TDF/FTC[a] **(AI)** or TAF/FTC[b] **(AII)** |
| **Alternative Regimen Options**<br>Alternative regimens are effective and tolerable, but have potential disadvantages when compared with the Recommended regimens, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials. **However, an Alternative regimen may be the preferred regimen for some patients.** |
| NNRTI plus 2 NRTIs:<br>• EFV/TDF/FTC[a] **(BI)**<br>• EFV plus TAF/FTC[b] **(BII)**<br>• RPV/TDF/FTC[a] **(BI)** or RPV/TAF/FTC[b] **(BII)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm$^3$**<br><br>Boosted PI plus 2 NRTIs:<br>• (ATV/c or ATV/r) plus either TDF/FTC[a] **(BI)** or TAF/FTC[b] **(BII)**<br>• DRV/c **(BIII)** or DRV/r **(BII)** plus ABC/3TC[a]—if HLA-B*5701 negative<br>• DRV/c plus either TDF/FTC[a] **(BII)** or TAF/FTC[b] **(BII)** |



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**Table 6. Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-Naive Patients (page 2 of 2)**

| Other Regimen Options |
|---|
| When compared with Recommended and Alternative regimens, Other regimens may have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as greater toxicities, higher pill burden, drug interaction potential, or limitations for use in certain patient populations. |
| If HIV RNA <100,000 copies/mL and HLA-B*5701 Negative:<br>• ATV/c **(CIII)** or ATV/r **(CI)** plus ABC/3TC<br>• EFV plus ABC/3TC[a] **(CI)**<br>• RAL plus ABC/3TC[a] **(CII)**<br><br>Other Regimens to Consider when TAF, TDF, or ABC Cannot be Used:<br>• DRV/r plus RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm$^3$**<br>• LPV/r plus 3TC[a] (BID) **(CI)** |

[a] 3TC may be substituted for FTC, or vice versa, if a non-fixed dose NRTI combination is desired.

[b] The evidence supporting this regimen is based on relative bioavailability data coupled with data from randomized, controlled switch trials demonstrating the safety and efficacy of TAF-containing regimens.

**Note:** The following are available as coformulated products: ABC/3TC, ATV/c, DRV/c, DTG/ABC/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, LPV/r, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, and TDF/FTC.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate



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**Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 1 of 4)**

This table is designed to guide clinicians in choosing an initial ARV regimen according to various patient and regimen characteristics and specific clinical scenarios. When more than one scenario applies to a patient, clinicians should review considerations for each relevant scenario and use their clinical judgment to select the most appropriate regimen. This table is intended to guide the initial choice of regimen. However, if a patient is doing well on a particular regimen, it is not necessary to switch to another regimen based on the scenarios outlined in this table. Please see Table 8 for additional information regarding the advantages and disadvantages of particular ARV medications.

| Patient or Regimen Characteristics | Clinical Scenario | Consideration(s) | Rationale/Comments |
|---|---|---|---|
| **Pre-ART Characteristics** | CD4 count <200 cells/ $mm^3$ | **Do Not Use the Following Regimens:**<br>• RPV-based regimens<br>• DRV/r plus RAL | Higher rate of virologic failure observed in those with low pretreatment CD4 cell count. |
| | HIV RNA >100,000 copies/mL | **Do Not Use the Following Regimens:**<br>• RPV-based regimens<br>• ABC/3TC with EFV or ATV/r<br>• DRV/r plus RAL | Higher rates of virologic failure observed in those with high pretreatment HIV RNA. |
| | HLA-B*5701 positive | **Do not use ABC-containing regimen.** | Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA-B*5701 allele. |
| | Must treat before HIV drug resistance results available | **Avoid NNRTI-based regimens.**<br>Recommended ART Regimens:<br>• DRV/r plus TAF/FTC or TDF/FTC<br>• DTG plus TAF/FTC or TDF/FTC | Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance.<br>Resistance to DRV/r and DTG emerges slowly; transmitted resistance to DRV is rare and transmitted resistance to DTG has not been reported to date. |



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**Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 2 of 4)**

| Patient or Regimen Characteristics | Clinical Scenario | Consideration(s) | Rationale/Comments |
|---|---|---|---|
| **ART-Specific Characteristics** | One pill once daily regimen is desired | ART Options Include:<br>• DTG/ABC/3TC<br>• EFV/TDF/FTC<br>• EVG/c/TAF/FTC<br>• EVG/c/TDF/FTC<br>• RPV/TAF/FTC<br>• RPV/TDF/FTC | Do not use RPV-based regimens if HIV RNA >100,000 copies/mL and CD4 count <200/mm$^3$<br>Do not use a regimen including ABC if HLA-B*5701 positive<br>See Appendix B, Table 7 for recommendations on ARV dose modification in the setting of renal impairment. |
| | Food effects | Regimens that Can be Taken Without Regard to Food:<br>• RAL- or DTG-based regimens | Oral bioavailability of these regimens is not significantly affected by food. |
| | | Regimens that Should be Taken with Food:<br>• ATV/r or ATV/c-based regimens<br>• DRV/r or DRV/c-based regimens<br>• EVG/c/TAF/FTC<br>• EVG/c/TDF/FTC<br>• RPV-based regimens | Food improves absorption of these listed regimens. RPV-containing regimens should be taken with at least 390 calories of food. |
| | | Regimens that Should be Taken on an Empty Stomach:<br>• EFV-based regimens | Food increases EFV absorption and may increase CNS side effects. |
| **Presence of Other Conditions** | Chronic kidney disease (defined as eGFR <60 mL/min) | **Avoid TDF.**<br>Use ABC or TAF.<br>ABC may be used if HLA-B*5701 negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r).<br>TAF may be used if eGFR >30 mL/min<br>Other Options When ABC or TAF Cannot be Used (See Text for Discussion):<br>• LPV/r plus 3TC; *or*<br>• RAL plus DRV/r (if CD4 count >200 cells/mm$^3$, HIV RNA <100,000 copies/mL) | TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction reported in patients using TDF in conjunction with RTV-containing regimens.<br>TAF has less impact on renal function and lower rates of proteinuria than TDF.<br>ABC has not been associated with renal dysfunction.<br>See Appendix B, Table 7 for recommendations on ARV dose modification in patients with renal insufficiency. |
| | Liver disease with cirrhosis | Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease. | Refer to Appendix B, Table 7 for specific dosing recommendations.<br>Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease. |
| | Osteoporosis | **Avoid TDF.**<br>Use ABC or TAF.<br>ABC may be used if HLA-B*5701 negative. If HIV RNA >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r). | TDF is associated with decreases in bone mineral density along with renal tubulopathy, urine phosphate wasting and resultant osteomalacia.<br>TAF and ABC are associated with smaller declines in bone mineral density than TDF. |



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**Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 3 of 4)**

| Patient or Regimen Characteristics | Clinical Scenario | Consideration(s) | Rationale/Comments |
|---|---|---|---|
| **Presence of Other Conditions,** continued | Psychiatric illnesses | **Consider avoiding EFV- and RPV-based regimens.** | EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality. |
| | HIV-associated dementia (HAD) | **Avoid EFV-based regimens if possible.**<br>Favor DRV-based or DTG-based regimens. | EFV-related neuropsychiatric effects may confound assessment of ART's beneficial effects on improvement of HAD-related symptoms.<br>Theoretical CNS penetration advantage |
| | Narcotic replacement therapy required | **If patient is receiving methadone, consider avoiding EFV-based regimens.**<br>If EFV is used, an increase in methadone dose may be necessary. | EFV reduces methadone concentrations and may lead to withdrawal symptoms. |
| | High cardiac risk | **Consider avoiding ABC- and LPV/r -based regimens.** | Increased cardiovascular risk in some studies |
| | Hyperlipidemia | The Following ARV Drugs have been Associated with Dyslipidemia:<br>• PI/r or PI/c<br>• EFV<br>• EVG/c | DTG and RAL have fewer lipid effects.<br>TDF has been associated with more favorable lipid effects than ABC or TAF. |
| | Pregnancy | Refer to the Perinatal Guidelines. | |
| **Presence of Coinfections** | HBV infection | Use TDF or TAF, with FTC or 3TC, whenever possible.<br>If TDF and TAF are Contraindicated:<br>• For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/HIV Coinfection). | TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug active against HBV. |
| | HCV treatment required | Refer to recommendations in HCV/HIV Coinfection. | |
| | Treating TB disease with rifamycins | TAF is not recommended with any rifamycin-containing regimen.<br>If Rifampin is Used:<br>• EFV can be used without dosage adjustment<br>• If RAL is used, increase RAL dose to 800 mg BID.<br>• Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label).<br>If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen. | • Rifamycins may significantly reduce TAF exposure.<br>• Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PI, INSTI, and RPV.<br>• Rifampin has a less significant effect on EFV concentration than on other NNRTIs, PIs, and INSTIs.<br>• Rifabutin is a less potent inducer and is a good option for patients receiving non-EFV-based regimens.<br>Refer to Tables 19a, b, d and e for dosing recommendations for rifamycins used with different ARV agents. |



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**Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios (page 4 of 4)**

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ARV = antiretroviral; c = cobicistat; CKD = chronic kidney disease; CrCl = creatinine clearance; DRV/r = darunavir/ritonavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate



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**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 3)**

**Note:** All drugs within an ARV class are listed in alphabetical order.

| ARV Class | ARV Agent(s) | Advantage(s) | Disadvantage(s) |
|---|---|---|---|
| Dual-NRTI | ABC/3TC | • Coformulated with DTG | • May cause life-threatening hypersensitivity reaction in patients positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use.<br>• In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG.<br>• ABC use has been associated with cardiovascular disease and cardiac events in some, but not all, observational studies. |
| | TAF/FTC | • Coformulated with EVG/c or RPV<br>• Active against HBV<br>• Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than after initiation of TDF/FTC<br>• Safe in patients with eGFR ≥30 mL/min | • Fasting lipid levels, including LDL and HDL cholesterol and triglycerides, increased more in the TAF group than in the TDF group. Total cholesterol to HDL ratio was unchanged. |
| | TDF/FTC | • Coformulated with EFV, EVG/c, and RPV as STRs<br>• Active against HBV; recommended dual-NRTI for HIV/HBV coinfected patients<br>• Better virologic responses than with ABC/3TC in patients with baseline viral load ≥100,000 copies/mL when combined with ATV/r or EFV<br>• Associated with more favorable lipid effects than ABC or TAF | • Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency<br>• Osteomalacia has been reported as a consequence of proximal tubulopathy.<br>• Decreases BMD more than other NRTI combinations |
| INSTI | DTG | • Once-daily dosing<br>• Higher barrier to resistance than EVG or RAL<br>• Coformulated with ABC and 3TC<br>• No food requirement<br>• No CYP3A4 interactions | • Oral absorption of DTG can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.<br>• Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function<br>• UGT substrate; potential for drug interactions (see Table 19d)<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions) |
| | EVG/c | • Coformulated with TDF/FTC or TAF/FTC<br>• Once-daily dosing<br>• Compared with ATV/r, causes smaller increases in total and LDL cholesterol | • EVG/c/TDF/FTC is only recommended for patients with baseline CrCl ≥70 mL/min; this regimen should be discontinued if CrCl decreases to <50 mL/min.<br>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates.<br>• Oral absorption of EVG can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.<br>• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function.<br>• May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens<br>• Food requirement<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions) |



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**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 3)**

| ARV Class | ARV Agent(s) | Advantage(s) | Disadvantage(s) |
|---|---|---|---|
| **INSTI,** cont'd | **RAL** | • Compared to other INSTIs, has longest post-marketing experience<br>• No food requirement<br>• No CYP3A4 interactions | • Twice-daily dosing<br>• May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens<br>• Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported.<br>• Rare cases of severe hypersensitivity reactions (including SJS and TEN) have been reported.<br>• Oral absorption of RAL can be reduced by simultaneous administration with products containing polyvalent cations (eg, Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d.<br>• UGT substrate; potential for drug interactions (see Table 19d)<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions) |
| **NNRTIs** | **EFV** | • Once-daily dosing<br>• Coformulated with TDF/FTC<br>• Long-term clinical experience<br>• EFV-based regimens (except for EFV plus ABC/3TC) have well documented efficacy in patients with high HIV RNA. | • Transmitted resistance more common than with PIs and INSTIs<br>• Short-and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality<br>• Teratogenic in nonhuman primates; avoid use in women who are trying to conceive or who are sexually active and not using contraception<br>• Dyslipidemia<br>• Greater risk of resistance at the time of treatment failure than with PIs<br>• Skin rash<br>• Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a)<br>• Should be taken on an empty stomach (food increases drug absorption and CNS toxicities) |
| | **RPV** | • Once-daily dosing<br>• Coformulated with TDF/FTC and TAF/FTC<br>• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill size than other coformulated ARV drugs<br>• Compared with EFV:<br>  • Fewer discontinuations for CNS adverse effects<br>  • Fewer lipid effects<br>  • Fewer rashes | • Not recommended in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 count <200 cells/mm$^3$ because of higher rate of virologic failure in these patients<br>• Transmitted resistance more common than with PIs and INSTIs<br>• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimen containing EFV and two NRTIs<br>• Potential for CYP450 drug interactions (see Tables 18, 19b, and 20a)<br>• Meal requirement (>390 kcal)<br>• Requires acid for adequate absorption<br>  • Contraindicated with PPIs<br>  • Use with H2 antagonists or antacids with caution (see Table 19a for detailed dosing information).<br>• Use caution when coadministering with a drug known to increase the risk of Torsades de Pointes.<br>• Depression and suicidality |
| **PIs** | **ATV/c or ATV/r** | • Once-daily dosing<br>• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL<br>• PI resistance at the time of treatment failure uncommon with PK-enhanced PIs<br>• ATV/c and ATV/r have similar virologic activity and toxicity profiles | • Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice<br>• Food requirement<br>• Absorption depends on food and low gastric pH (see Table 19a for interactions with H2 antagonists, antacids, and PPIs)<br>• Nephrolithiasis, cholelithiasis, nephrotoxicity<br>• GI adverse effects<br>• CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a) |



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**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 3)**

| ARV Class | ARV Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| **PIs,** cont'd | **ATV/c**<br><br>(Specific considerations) | • Coformulated tablet | • COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function.<br>• Coadministration with TDF is not recommended in patients with CrCl <70 mL/min<br>• Less long-term clinical experience than for ATV/r<br>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. |
| | **DRV/c or DRV/r** | • Once-daily dosing<br>• Higher genetic barrier to resistance than NNRTIs, EVG, and RAL<br>• PI resistance at the time of treatment failure uncommon with PK-enhanced PIs | • Skin rash<br>• Food requirement<br>• GI adverse effects<br>• CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a) |
| | **DRV/c-specific considerations** | • Coformulated tablet | • Less long-term clinical experience than for DRV/r<br>• COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function.<br>• Coadministration with TDF is not recommended in patients with CrCl <70 mL/min<br>• Approval primarily based on PK data comparable to that for DRV/r rather than on trials comparing the efficacy of DRV/c and DRV/r<br>• COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. |
| | **LPV/r** | • Only RTV-coformulated PI<br>• No food requirement<br>• Once or twice daily dosing | • Requires 200 mg per day of RTV<br>• Possible higher risk of MI associated with cumulative use of LPV/r<br>• PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or in patients receiving other drugs with similar effect<br>• Possible nephrotoxicity<br>• CYP3A4 inhibitors and substrates: potential for drug interactions (see Tables 18 and 19a) |

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; Ca = calcium; $CaCO_3$ = calcium carbonate; CD4 = CD4 T lymphocyte; CNS = central nervous system; c or COBI= cobicistat; Cr = creatinine; CrCl = creatinine clearance; CYP = cytochrome P450; DRV darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; Mg = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STRs = single-tablet regimens; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis



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**Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 1 of 2)**

| ARV Drugs or Components | Reasons for Not Recommending as Initial Therapy |
|---|---|
| **NRTIs** | |
| **ABC/3TC/ZDV (Co-Formulated)**<br>As triple-NRTI combination regimen | • Inferior virologic efficacy |
| **ABC/3TC/ZDV plus TDF**<br>As quadruple-NRTI combination regimen | • Inferior virologic efficacy |
| **d4T plus 3TC** | • Significant toxicities including lipoatrophy, peripheral neuropathy, and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis |
| **ddI plus 3TC (or FTC)** | • Inferior virologic efficacy<br>• Limited clinical trial experience in ART-naive patients<br>• ddI toxicities such as pancreatitis, peripheral neuropathy |
| **ddI plus TDF** | • High rate of early virologic failure<br>• Rapid selection of resistance mutations<br>• Potential for immunologic nonresponse/CD4 cell decline<br>• Increased ddI drug exposure and toxicities |
| **ZDV/3TC** | • Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs. |
| **NNRTIs** | |
| **DLV** | • Inferior virologic efficacy<br>• Inconvenient (three times daily) dosing |
| **ETR** | • Insufficient data in ART-naive patients |
| **NVP** | • Associated with serious and potentially fatal toxicity (hepatic events, severe rash, including SJS and TEN)<br>• When compared to EFV, NVP did not meet noninferiority criteria |
| **PIs** | |
| **ATV (Unboosted)** | • Less potent than boosted ATV |
| **DRV (Unboosted)** | • Use without RTV or COBI has not been studied |
| **FPV (Unboosted)**<br>or<br>**FPV/r** | • Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV.<br>• Less clinical trial data for FPV/r than for other PI/r |
| **IDV (Unboosted)** | • Inconvenient dosing (three times daily with meal restrictions)<br>• Fluid requirement<br>• IDV toxicities such as nephrolithiasis, crystalluria |
| **IDV/r** | • Fluid requirement<br>• IDV toxicities such as nephrolithiasis, crystalluria |
| **LPV/r plus 2 NRTI** | • Higher pill burden than other PI-based regimens<br>• Higher ritonavir dose than other PI-based regimens<br>• GI intolerance |



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**Table 9. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 2 of 2)**

| ARV Drugs or Components | Reasons for Not Recommending as Initial Therapy |
|---|---|
| **NFV** | • Inferior virologic efficacy<br>• Diarrhea |
| **RTV as sole PI** | • High pill burden<br>• GI intolerance<br>• Metabolic toxicity |
| SQV (**Unboosted**) | • Inadequate bioavailability<br>• Inferior virologic efficacy |
| **SQV/r** | • High pill burden<br>• Can cause QT and PR prolongation; requires pretreatment and follow-up ECG |
| **TPV/r** | • Inferior virologic efficacy<br>• Higher rate of adverse events than other RTV-boosted PIs<br>• Higher dose of RTV required for boosting than other RTV-boosted PIs |
| **CCR5 Anagonist** | |
| **MVC** | • Requires testing for CCR5 tropism before initiation of therapy<br>• No virologic benefit when compared with other recommended regimens<br>• Requires twice-daily dosing |

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; COBI= cobicistat; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; IDV = indinavir; IDV/r = indinavir/ritonavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine



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**Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 1 of 2)**

| | Rationale | Exception |
|---|---|---|
| **Antiretroviral Regimens Not Recommended** | | |
| **Monotherapy with NRTI (AII)** | • Rapid development of resistance<br>• Inferior ARV activity when compared with combination of three or more ARV agents | • No exception |
| **Dual-NRTI regimens (AI)** | • Rapid development of resistance<br>• Inferior ARV activity when compared with combination of three or more ARV agents | • No exception |
| **Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)** | • High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naive patients.<br>• Other triple-NRTI regimens have not been evaluated. | • ABC/ZDV/3TC **(BI)** and possibly TDF + ZDV/3TC **(BII)** in patients in whom other combinations are not desirable |
| **Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen** | | |
| **ATV + IDV (AIII)** | • Potential additive hyperbilirubinemia | • No exception |
| **ddI + d4T (AII)** | • High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia<br>• Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women | • No exception |
| **ddI + TDF (AII)** | • Increased ddI concentrations and serious ddI-associated toxicities<br>• Potential for immunologic nonresponse and/or CD4 cell count decline<br>• High rate of early virologic failure<br>• Rapid selection of resistance mutations at failure | • Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination. |
| **2-NNRTI combination (AI)** | • When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen.<br>• Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR. | • No exception |
| **EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)** | • Teratogenic in nonhuman primates | • When no other ARV options are available and potential benefits outweigh the risks **(BIII)** |
| **FTC + 3TC (AIII)** | • Similar resistance profiles<br>• No potential benefit | • No exception |
| **ETR + unboosted PI (AII)** | • ETR may induce metabolism of these PIs; appropriate doses not yet established | • No exception |
| **ETR + RTV-boosted ATV or FPV (AII)** | • ETR may alter the concentrations of these PIs; appropriate doses not yet established | • No exception |
| **ETR + RTV-boosted TPV (AII)** | • ETR concentration may be significantly reduced by RTV-boosted TPV | • No exception |



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**Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 2 of 2)**

| | Rationale | Exception |
|---|---|---|
| **NVP in ARV-naive women with CD4 count >250 cells/mm$^3$ or men with CD4 count >400 cells/mm$^3$ (BI)** | • High incidence of symptomatic hepatotoxicity | • If no other ARV option available; if used, patient should be closely monitored |
| **d4T + ZDV (AII)** | • Antagonistic effect on HIV-1 | • No exception |
| **Unboosted DRV, SQV, or TPV (AII)** | • Inadequate bioavailability | • No exception |

**Acronyms:** 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emitricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine



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## Table 11. Identifying, Diagnosing, and Managing Acute and Recent HIV-1 Infection

Suspicion of Acute HIV-1 Infection:

- Acute HIV-1 infection should be considered in individuals with signs or symptoms described below and recent (within 2 to 6 weeks) high risk of exposure to HIV-1.[a]
- Signs, symptoms, or laboratory findings of acute HIV-1 infection may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
- High-risk exposures include sexual contact with an HIV-1-infected person or a person at risk of HIV-1 infection, sharing of injection drug use paraphernalia, or any exposure in which an individual's mucous membranes or breaks in the skin come in contact with bodily fluid potentially infected with HIV.
- **Differential diagnosis:** The differential diagnosis of patients presenting with HIV-1 infection may include but is not limited to viral illnesses such as Epstein-Barr virus (EBV) and non-EBV (e.g., cytomegalovirus) infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, or syphilis.

Evaluation/Diagnosis of Acute HIV-1 Infection:

- Acute HIV-1 infection is defined as detectable HIV-1 RNA or p24 antigen (the antigen used in currently available HIV antigen/antibody [Ag/Ab] combination assays) in the setting of a negative or indeterminate HIV-1 antibody test result.
- A reactive HIV antibody test result or Ag/Ab combination test result must be followed by supplemental confirmatory testing.
- A negative or indeterminate HIV-1 antibody test result in a person with a reactive Ag/Ab test result or in whom acute HIV-1 infection is suspected requires plasma HIV-1 RNA testing to diagnose acute HIV-1 infection.
- A positive result on a quantitative or qualitative plasma HIV-1 RNA test in the setting of a negative or indeterminate antibody test result indicates that acute HIV-1 infection is highly likely.

ART After Diagnosis of Early HIV-1 Infection:

- ART is recommended for all HIV-infected individuals **(AI)**, and should be offered to all patients with early HIV-1 infection.
- All pregnant women with early HIV-1 infection should begin ART as soon as possible for their health and to prevent perinatal transmission of HIV-1.
- Genotypic drug resistance testing should be performed before initiation of ART to guide the selection of the regimen **(AII)**.
- If ART is initiated before drug resistance test results are available, a pharmacologically boosted PI-based regimen is recommended because resistance to PIs emerges slowly and clinically significant transmitted resistance to PIs is uncommon. DRV/r plus TDF/FTC is a recommended regimen in this setting **(AIII)**. For similar reasons, DTG plus TDF/FTC is a reasonable option although the data regarding transmission of INSTI-resistant HIV and the efficacy of this regimen in early HIV infection are limited **(AIII)**.
- When results of drug resistance testing are available, the treatment regimen can be modified if warranted **(AII)**. In patients without transmitted drug-resistant virus, ART should be initiated with one of the combination regimens that is recommended for patients with chronic HIV-1 infection (see What to Start) **(AIII)**.
- Once initiated, the goal of ART should be sustained plasma virologic suppression; ART should be continued indefinitely **(AIII)**.

[a] In some settings, behaviors that increase the risk of HIV-1 infection may not be recognized or perceived as risky by the health care provider or the patient or both. Thus, even in the absence of reported high-risk behaviors, symptoms and signs consistent with acute retroviral syndrome should motivate practitioners to consider a diagnosis of acute HIV-1 infection.

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; DRV/r = darunavir/ritonavir; DTG = dolutegravir; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; TDF/FTC = tenofovir disoproxil fumerate/emtricitabine



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**Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults** (page 1 of 3)

The recommendations in this table for concomitant use of selected HIV drugs with FDA-approved HCV direct-acting antiviral (DAA) drugs are based on available pharmacokinetics interaction data or predictions based on the known metabolic pathway of the agents. In some cases, there are not enough data to make any recommendations, and these instances are indicated in the table. In all cases where HIV and HCV drugs are used concomitantly, patients should be closely monitored for HIV and HCV virologic efficacy and potential toxicities. As the field of HCV therapy is rapidly evolving, readers should also refer to the latest drug product labels and HCV guidelines (www.hcvguidelines.org/) for updated information.

| Selected HIV Drugs | HCV DAA Drugs | | | | | |
|---|---|---|---|---|---|---|
| | NS5A Inhibitor | NS5B Inhibitor | Coformulated NS5A/NS5B Inhibitor | Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor | Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor | NS3A/4A Protease Inhibitor[a] |
| | Daclatasvir | Sofosbuvir | Ledipasvir/ Sofosbuvir | Elbasvir/ Grazoprevir | Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir[b] | Simeprevir |
| **Nucleoside Reverse Transcriptase Inhibitors** | | | | | | |
| 3TC | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| ABC | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| FTC | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| TDF | ✓ | ✓ | ✓<br>Monitor for TDF toxicity. | ✓ | ✓ | ✓ |
| TAF | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **HIV Protease Inhibitors** | | | | | | |
| ATV (unboosted) | ✓ | ✓ | ✓ | × | ✓<br>Reduce ATV dose to 300 mg and take in the morning at same time as ombitasvir/ paritaprevir/ritonavir plus dasabuvir.<br>If RTV cannot be used, choose an alternative HCV regimen. | × |



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**Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults** (page 2 of 3)

| Selected HIV Drugs | HCV DAA Drugs | | | | | |
|---|---|---|---|---|---|---|
| | NS5A Inhibitor | NS5B Inhibitor | Coformulated NS5A/NS5B Inhibitor | Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor | Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor | NS3A/4A Protease Inhibitor[a] |
| | Daclatasvir | Sofosbuvir | Ledipasvir/ Sofosbuvir | Elbasvir/ Grazoprevir | Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir | Simeprevir |
| **HIV Protease Inhibitors**, continued | | | | | | |
| ATV/r or ATV/c | ✓ ↓ DCV dose to 30 mg/day | ✓ | ✓ If PI/r (or ATV/c, DRV/c) is used with TDF, ↑TDF concentrations are expected. If coadministration necessary, monitor for TDF-associated toxicities (see footnote[c]). | × | ✓ Take ATV 300 mg in the morning at same time as ombitasvir/ paritaprevir/r plus dasubuvir; discontinue RTV or COBI in HIV regimen until HCV therapy completed. | × |
| DRV/r or DRV/c | ✓ | ✓ | | × | × | × |
| FPV or FPV/r | ✓ | ✓ | | × | × | × |
| LPV/r | ✓ | ✓ | | × | × | × |
| SQV/r | ✓ ↓ DCV dose to 30 mg/day | | | × | × | × |
| TPV/r | ? | × | × | × | × | × |
| **Non-Nucleoside Reverse Transcriptase Inhibitors** | | | | | | |
| EFV | ✓ ↑ DCV dose to 90 mg/day | ✓ | ✓ If used with TDF, monitor for TDF toxicity. | × | × | × |
| ETR | ↑ DCV dose to 90 mg/day | ✓ | | × | × | × |
| NVP | ↑ DCV dose to 90 mg/day | ✓ | | × | × | × |
| RPV | ✓ | ✓ | | ✓ | × | ✓ |



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**Table 12. Concomitant Use of Selected HIV Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of Hepatitis C in HIV-Infected Adults** (page 3 of 3)

| Selected HIV Drugs | HCV DAA Drugs | | | | | |
|---|---|---|---|---|---|---|
| | NS5A Inhibitor | NS5B Inhibitor | Coformulated NS5A/NS5B Inhibitor | Coformulated NS5A Inhibitor/ NS3A/4A Protease Inhibitor | Coformulated NS5A/NS3A/4A Protease Inhibitor plus NS5B Inhibitor | NS3A/4A Protease Inhibitor[a] |
| | Daclatasvir | Sofosbuvir | Ledipasvir/ Sofosbuvir | Elbasvir/ Grazoprevir | Ombitasvir/ Paritaprevir/ Ritonavir plus Dasabuvir | Simeprevir |
| **Integrase Strand Transfer Inhibitors** | | | | | | |
| **DTG** | ✓ | ✓ | ✓<br>If used with TDF, monitor for TDF toxicity. | ✓ | ✓ | ✓ |
| **EVG/c/TDF/FTC** | ✓<br>↓ DCV dose to 30 mg/day | ✓ | × | × | × | × |
| **EVG/c/TAF/FTC** | ✓<br>↓ DCV dose to 30 mg/day | ✓ | ✓ | × | × | × |
| **EVG (plus PI/r without COBI)** | ✓<br>↓ DCV dose to 30 mg/day for all PI/r, except TPV/r — do not coadminister | Refer to Recommendations for individual ritonavir-boosted PI. | | | | |
| **RAL** | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **CCR5 Antagonist** | | | | | | |
| **MVC** | ✓ | ✓ | ✓ | ? | × | ✓ |

[a] Since boceprevir is no longer recommended for HCV treatment and telaprevir is no longer available in the United States, these products have been removed from this table.

[b] Dasabuvir must be prescribed with ombitasvir/paritaprevir/ritonavir.

[c] Consider alternative HCV or ARV therapy to avoid increases in TDF exposure. If coadministration is necessary, monitor for TDF-associated adverse reactions.

**Key to Symbols:** ✓ = ARV agents that can be used concomitantly

× = ARV agents not recommended

? = data limited or not available on PK interactions with ARV drug

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; c or COBI = cobicistat; DAA = direct-acting antiviral agents; DCV = daclatasvir; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine



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**Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care**
(page 1 of 3)

| Strategies | Examples |
|---|---|
| Use a multidisciplinary team approach.<br><br>Provide an accessible, trustworthy health care team. | • Nonjudgmental providers, nurses, social workers, pharmacists, and medication managers |
| Strengthen early linkage to care and retention in care. | • Encourage healthcare team participation in linkage to and retention in care. |
| Assess patient readiness to start ART. | |
| Evaluate patient's knowledge about HIV disease, prevention and treatment and, on the basis of the assessment, provide HIV-related information. | • Considering the patient's current knowledge base, provide information about HIV, including the natural history of the disease, HIV viral load and CD4 count and expected clinical outcomes according to these parameters, and therapeutic and prevention consequences of non-adherence. |
| Identify facilitators, potential barriers to adherence, and necessary medication management skills before starting ART medication. | • Assess patient's cognitive competence and impairment.<br>• Assess behavioral and psychosocial challenges including depression, mental illnesses, levels of social support, high levels of alcohol consumption and active substance use, non-disclosure of HIV serostatus and stigma.<br>• Identify and address language and literacy barriers.<br>• Assess beliefs, perceptions, and expectations about taking ART (e.g., impact on health, side effects, disclosure issues, consequences of non-adherence).<br>• Ask about medication taking skills and foreseeable challenges with adherence (e.g., past difficulty keeping appointments, adverse effects from previous medications, issues managing other chronic medications, need for medication reminders and organizers).<br>• Assess structural issues including unstable housing, lack of income, unpredictable daily schedule, lack of prescription drug coverage, lack of continuous access to medications. |
| Provide needed resources. | • Provide or refer for mental health and/or substance abuse treatment.<br>• Provide resources to obtain prescription drug coverage, stable housing, social support, and income and food security. |



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**Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care**
(page 2 of 3)

| Strategies | Examples |
|---|---|
| Involve the patient in ARV regimen selection. | • Review regimen potency, potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence.<br>• Assess daily activities and tailor regimen to predictable and routine daily events.<br>• Consider preferential use of PI/r-based ART if poor adherence is predicted.<br>• Consider use of fixed-dose combination formulation.<br>• Assess if cost/co-payment for drugs can affect access to medications and adherence. |
| Assess adherence at every clinic visit. | • Monitor viral load as a strong biologic measure of adherence.<br>• Use a simple behavioral rating scale.<br>• Employ a structured format that normalizes or assumes less-than-perfect adherence and minimizes socially desirable or "white coat adherence" responses.<br>• Ensure that other members of the health care team also assess adherence. |
| Use positive reinforcement to foster adherence success. | • Inform patients of low or non-detectable levels of HIV viral load and increases in CD4 cell counts.<br>• When needed, consider providing incentives and rewards for achieving high levels of adherence and treatment success. |
| Identify the type of and reasons for nonadherence. | • Failure to fill the prescription(s)<br>• Failure to understand dosing instructions<br>• Complexity of regimen (e.g., pill burden, size, dosing schedule, food requirements)<br>• Pill aversion<br>• Pill fatigue<br>• Adverse effects<br>• Inadequate understanding of drug resistance and its relationship to adherence<br>• Cost-related issues<br>• Depression, drug and alcohol use, homelessness, poverty<br>• Stigma<br>• Non-disclosure<br>• Other potential barriers |
| Select from among available effective treatment adherence interventions. | • See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm.<br>• Use adherence-related tools to complement education and counseling interventions (e.g., pill boxes, dose planners, reminder devices).<br>• Use community resources to support adherence (e.g., visiting nurses, community workers, family, peer advocates).<br>• Use patient prescription assistance programs.<br>• Use motivational interviews. |



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**Table 13. Strategies to Improve Adherence to Antiretroviral Therapy and Retention in Care**
(page 3 of 3)

| Strategies | Examples |
|---|---|
| Systematically monitor retention in care. | • Record and follow up on missed visits. |
| On the basis of any problems identified through systematic monitoring, consider options to enhance retention in care given resources available. | • Provide outreach for those patients who drop out of care.<br>• Use peer or paraprofessional treatment navigators.<br>• Employ incentives to encourage clinic attendance or recognize positive clinical outcomes resulting from good adherence.<br>• Arrange for directly observed therapy (if feasible). |

**Key to Acronyms:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor



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## Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 5)

N/A indicates either that there are no reported cases for the particular side effect or that data for the specific ARV drug class are not available. See Appendix B for additional information listed by drug.

| Adverse Effect | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Bleeding Events** | N/A | N/A | Spontaneous bleeding, hematuria in hemophilia.<br><br>**TPV:** Intracranial hemorrhage associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anticoagulant or antiplatelet agents, vitamin E | N/A | N/A |
| **Bone Density Effects** | **TDF:** Associated with greater loss of BMD than other NRTIs; osteomalacia may be associated with renal tubulopathy and urine phosphate wasting<br><br>**TAF:** Smaller declines in BMD than with TDF. | Decreases in BMD observed after the initiation of any ART regimen. | | | N/A |
| **Bone Marrow Suppression** | **ZDV:** Anemia, neutropenia | N/A | N/A | N/A | N/A |
| **Cardiovascular Disease** | **ABC and ddI:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors. | **RPV:** QTc prolongation | Associated with MI and stroke in some cohorts.<br><br>**SQV/r, ATV/r, and LPV/r:** PR prolongation (risks include pre-existing heart disease, other medications).<br><br>**SQV/r:** QT prolongation. Obtain ECG before administering SQV. | N/A | N/A |
| **Cholelithiasis** | N/A | N/A | **ATV:** Cholelithiasis and kidney stones may present concurrently.<br><br>Median onset is 42 months. | N/A | N/A |
| **Diabetes Mellitus/ Insulin Resistance** | ZDV, d4T, and ddI | N/A | Reported for some (IDV, LPV/r), but not all PIs | N/A | N/A |



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**Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 5)**

| Adverse Effect | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Dyslipidemia** | **d4T > ZDV > ABC:** ↑TG and LDL<br><br>**TAF > TDF:** ↑TG, ↑LDL, ↑HDL (no change in TC:HDL ratio) | **EFV:** ↑TG, ↑LDL, ↑HDL | **All RTV- or COBI-boosted PIs:** ↑TG, ↑LDL, ↑HDL<br><br>**LPV/r = FPV/r and LPV/r > DRV/r and ATV/r:** ↑TG | **EVG/c:** ↑TG, ↑LDL, ↑HDL | N/A |
| **Gastrointestinal Effects** | **ddI and ZDV > other NRTIs:** Nausea and vomiting<br><br>**ddI:** Pancreatitis | N/A | GI intolerance (eg, diarrhea, nausea, vomiting)<br><br>**Common with LPV/r and more frequent than with DRV/r and ATV/r:** Diarrhea | **EVG/c:** Nausea and diarrhea | N/A |
| **Hepatic Effects** | Reported with most NRTIs.<br><br>**ZDV, d4T, or ddI:** Steatosis most common<br><br>**ddI:** Prolonged exposure linked to noncirrhotic portal hypertension, esophageal varices.<br><br>**When TAF, TDF, 3TC, and FTC are withdrawn or when HBV resistance develops:** HIV/HBV-coinfected patients may develop severe hepatic flares. | NVP > other NNRTIs<br><br>**NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. Two-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count >250 cells/mm$^3$ and men with pre-NVP CD4 count >400 cells/mm$^3$. NVP should **never** be used for postexposure prophylaxis, or in patients with hepatic insufficiency (Child-Pugh B or C). | **All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency with TPV/r.<br><br>**IDV, ATV:** Jaundice due to indirect hyperbilirubinemia<br><br>**TPV/r: Contraindicated** in patients with hepatic insufficiency (Child-Pugh B or C) | N/A | **MVC:** Hepatotoxicity with or without rash or HSRs reported |



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**Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 5)**

| Adverse Effect | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Hypersensitivity Reaction**<br><br>Excluding rash alone or Stevens-Johnson syndrome | **ABC: Contraindicated** if HLA-B*5701 positive. Median onset 9 days; 90% of reactions occur within first 6 weeks of treatment.<br><br>HSR symptoms (in order of descending frequency): fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms.<br><br>Symptoms worsen with continuation of ABC.<br><br>Patients, regardless of HLA-B*5701 status, should not be rechallenged with ABC if HSR is suspected. | **NVP:** Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy.<br><br>Risk is greater for ARV-naive women with pre-NVP CD4 count >250 cells/$mm^3$ and men with pre-NVP CD4 count >400 cells/$mm^3$. Overall, risk is higher for women than men.<br><br>Two-week dose escalation of NVP reduces risk. | N/A | **RAL:** HSR reported when RAL given in combination with other drugs known to cause HSR. All ARVs should be stopped if HSR occurs.<br><br>**DTG:** Reported in <1% of patients in clinical development program | **MVC:** Reported as part of a syndrome related to hepatotoxicity |
| **Lactic Acidosis** | **Reported with NRTIs, especially d4T, ZDV, and ddI:** Insidious onset with GI prodrome, weight loss, and fatigue. May rapidly progress with tachycardia, tachypnea, jaundice, weakness, mental status changes, pancreatitis, and organ failure. Mortality high if serum lactate >10 mmol/L.<br><br>Women and obese patients at increased risk. | N/A | N/A | N/A | N/A |



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**Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 5)**

| Adverse Effect | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Lipodystrophy** | **Lipoatrophy:** d4T > ZDV. May be more likely when NRTIs combined with EFV than with an RTV-boosted PI. | Lipohypertophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established. | | | N/A |
| **Myopathy/ Elevated Creatine Phosphokinase** | **ZDV:** Myopathy | N/A | N/A | **RAL:** ↑CPK, weakness and rhabdomyolysis | N/A |
| **Nervous System/ Psychiatric Effects** | **d4T > ddI and ddC:** Peripheral neuropathy: (can be irreversible).<br>**d4T:** Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare). | **EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2 to 4 weeks. Bedtime dosing may reduce symptoms. Risks include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among younger patients and those with history of mental illness or substance abuse) was found in a retrospective analysis of comparative trials.<br>**RPV:** Depression, suicidality, sleep disturbances | N/A | **All INSTIs:** Insomnia, depression, and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions. | N/A |
| **Rash** | **FTC:** Hyperpigmentation | All NNRTIs | ATV, DRV, FPV, LPV/r, TPV | RAL, EVG | MVC |



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**Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 5)**

| Adverse Effect | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Renal Effects/ Urolithiasis** | **TDF:** ↑SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis. Concurrent use of TDF with COBI or RTV-containing regimens appears to increase risk.<br><br>**TAF:** Less impact on renal biomarkers and lower rates of proteinuria than TDF. | N/A | **ATV and LPV/r:** Increased risk of chronic kidney disease in a large cohort study.<br><br>**IDV:** ↑SCr, pyuria, renal atrophy or hydronephrosis<br><br>**IDV, ATV:** Stone, crystal formation; adequate hydration may reduce risk. | **COBI and DTG:** Inhibits Cr secretion without reducing renal glomerular function. | N/A |
| **Stevens-Johnson Syndrome/Toxic Epidermal Necrosis** | **ddI, ZDV:** Reported cases | NVP > DLV, EFV, ETR, RPV | **FPV, DRV, IDV, LPV/r, ATV:** Reported cases | RAL | N/A |

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CrCl = creatinine clearance; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine



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**Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 1 of 2)**

| Adverse Event | ARV Agent(s) or Drug Class | | Comments |
|---|---|---|---|
| | Switch from | Switch to | |
| **Bone Density Effects** | TDF[a] | ABC[b] or TAF<br>NRTI-sparing regimens or regimens using only 3TC or FTC as NRTI may be considered if appropriate. | Declines in BMD have been observed upon initiation of most ART regimens. Switching from TDF to alternative ARV agents has been shown to increase bone density, but the clinical significance of this increase remains uncertain.<br>TAF is associated with smaller declines in BMD than TDF, and with improvement in BMD upon switching from TDF. The long-term impact of TAF on patients with osteopenia or osteoporosis is unknown; close clinical monitoring is recommended in this setting. |
| **Bone Marrow Suppression** | ZDV | TDF, TAF, or ABC[b] | ZDV has been associated with neutropenia and macrocytic anemia. |
| **Central Nervous System, Neuropsychiatric Side Effects**<br>Dizziness, suicidal ideation, abnormal dreams, depression | EFV, RPV | ETR or a PI/c or PI/r<br>INSTIs may be considered (see Comments column). | In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV.<br>INSTIs are associated with insomnia. Depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions. |
| **Dyslipidemia**<br>Hypertriglyceridemia (with or without elevated LDL level) | RTV- or COBI-boosted regimens; EFV; EVG/c | RAL, DTG, RPV | Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c] |
| **Gastrointestinal Effects**<br>Nausea, diarrhea | LPV/r | ATV/c, ATV/r, DRV/c, DRV/r, RAL, DTG, EVG/c | GI intolerance is common with boosted PIs and is linked to the total dose of RTV. More GI toxicity is seen with LPV/r than with ATV/r or DRV/r. GI effects are often transient, and do not warrant substitution unless persistent and intolerable. |
| | Other RTV- or COBI-boosted regimens | RAL, DTG, NNRTIs | In a trial of treatment-naive patients, rates of diarrhea and nausea were similar for EVG/c/TDF/FTC and ATV/r plus TDF/FTC. |
| **Hypersensitivity Reaction** | ABC | TDF or TAF | Never rechallenge with ABC following a suspected HSR, regardless of the patient's HLA-B*5701 status. |
| | NVP, EFV, ETR, RPV | Non-NNRTI ART | Risk of HSR with NVP is higher for women and those with high CD4 cell counts. |
| | DTG, RAL<br>MVC | Non-INSTI ART<br>Suitable alternative ART | Reactions to NVP, ETR, RAL, DTG and MVC may be accompanied by elevated liver transaminases. |
| **Insulin Resistance** | LPV/r, FPV/r | INSTI, RPV | Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r (and IDV) on insulin resistance. However, traditional risk factors may be stronger risk factors for insulin resistance than use of any PI. |
| **Jaundice and Icterus** | ATV, ATV/c, ATV/r | DRV/c, DRV/r, INSTI, or NNRTI | Increases in unconjugated bilirubin are common with ATV and generally do not require modification of therapy unless resultant symptoms are distressing to the patient. |



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**Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent (page 2 of 2)**

| Adverse Event | ARV Agent(s) or Drug Class | | Comments |
|---|---|---|---|
| | Switch from | Switch to | |
| **Lipoatrophy**<br>Subcutaneous fat wasting of limbs, face, buttocks | d4T, ZDV | TDF, TAF, or ABC[b] | Peripheral lipoatrophy is a legacy of prior thymidine analog (d4T and ZDV) use. Switching from these ARVs prevents worsening lipoatrophy, but fat recovery is typically slow (may take years) and incomplete. |
| **Lipohypertrophy** | Accumulation of visceral, truncal, dorso-cervical, and breast fat has been observed during ART, particularly during use of older PI-based regimens (eg, IDV), but whether ART directly causes fat accumulation remains unclear. There is no clinical evidence that switching to another first line regimen will reverse weight or visceral fat gain. | | |
| **Rash** | NNRTIs (especially NVP and EFV) | PI- or INSTI-based regimen | Mild rashes developing after initiation of NNRTIs other than NVP rarely require treatment switch. When serious rash develops due to any NNRTI, switch to another drug class. |
| | DRV/c, DRV/r | ATV/c, ATV/r, or another drug class (eg, INSTI) | Mild rashes following DRV/r use may resolve with close follow-up only. For more severe reactions, change to an alternative boosted PI or an agent from another drug class. |
| **Renal Effects**<br>Including proximal renal tubulopathy, elevated creatinine | TDF[a] | ABC[b] or<br>TAF (for patients with CrCl >30mL/min) or NRTI-sparing regimens, or regimens using only 3TC or FTC as NRTI may be considered if appropriate. | TDF may cause tubulopathy.<br>Switching from TDF to TAF is associated with improvement in proteinuria and renal biomarkers. The long-term impact of TAF on patients with pre-existing renal disease, including overt proximal tubulopathy, is unknown, and close clinical monitoring is recommended in this setting. |
| | ATV/c, ATV/r, LPV/r | DTG, RAL, or NNRTI | COBI and DTG, and to a lesser extent RPV, can increase SCr through inhibition of creatinine secretion. This effect does not affect glomerular filtration. However, assess for renal dysfunction if SCr increases by >0.4 mg/dL. |
| **Stones**<br>Nephrolithiasis and cholelithiasis | ATV, ATV/c, ATV/r | DRV/c, DRV/r, INSTI, or NNRTI | Assuming that ATV is believed to be causing the stones. |

[a] In patients with chronic active HBV infection, another agent active against HBV should be substituted for TDF.

[b] ABC should be used only in patients known to be HLA-B*5701 negative.

[c] TDF reduces ATV levels; therefore, unboosted ATV should not be co-administered with TDF. Long-term data for unboosted ATV are unavailable.

**Key to Abbreviations:** ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; CNS = central nervous system; COBI or c = cobicistat; d4T = stavudine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine



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**Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 4)**

| ARV Drug (Generic and Brand Names) | Strength Formulation | Dosing | Tablets, Capsules, or mLs per Month[a] | AWP[b] (Monthly) |
|---|---|---|---|---|
| **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** | | | | |
| **Abacavir** | | | | |
| • Generic | 300 mg tablet | 2 tablets daily | 60 tablets | $602.66 |
| • Ziagen | 300 mg tablet | 2 tablets daily | 60 tablets | $670.37 |
| • Ziagen | 20 mg/mL solution | 30 mL daily | 900 mL | $660.86 |
| **Emtricitabine** | | | | |
| • Emtriva | 200 mg capsules | 1 capsule daily | 30 capsules | $643.82 |
| • Emtriva | 10 mg/mL solution | 24 mL daily | 680 mL (28-day supply) | $643.82 |
| **Lamivudine** | | | | |
| • Generic | 300 mg tablet | 1 tablet daily | 30 tablets | $283.89 |
| • Epivir | 300 mg tablet | 1 tablet daily | 30 tablets | $498.89 |
| • Epivir | 10 mg/mL solution | 30 mL daily | 900 mL | $498.90 |
| **Tenofovir Disoproxil Fumarate** | | | | |
| • Viread | 300 mg tablet | 1 tablet daily | 30 tablets | $1,197.32 |
| **Zidovudine** | | | | |
| • Generic | 300 mg tablet | 1 tablet twice daily | 60 tablets | $54.00–$360.97 |
| **NRTI Combination Products** | | | | |
| **Abacavir/Lamivudine** | | | | |
| • Epzicom | 600/300 mg tablets | 1 tablet daily | 30 tablets | $1,550.05 |
| **Tenofovir Alafenamide /Emtricitabine** | | | | |
| • Descovy | 25/200 mg tablet | 1 tablet daily | 30 tablets | $1,759,73 |
| **Tenofovir Disoproxil Fumarate/Emtricitabine** | | | | |
| • Truvada | 300/200 mg tablet | 1 tablet daily | 30 tablets | $1,759.73 |



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**Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 4)**

| ARV Drug (Generic and Brand Names) | Strength Formulation | Dosing | Tablets, Capsules, or mLs per Month[a] | AWP[b] (Monthly) |
|---|---|---|---|---|
| **Zidovudine/Lamivudine** | | | | |
| • Generic | 300/150 mg tablet | 1 tablet twice daily | 60 tablets | $877.85 |
| • Combivir | 300/150 mg tablet | 1 tablet twice daily | 60 tablets | $1,081.70 |
| **Abacavir Sulfate/Zidovudine/ Lamivudine** | | | | |
| • Generic | 300/300/150 mg tablet | 1 tablet twice daily | 60 tablets | $1,738.46 |
| • Trizivir | 300/300/150 mg tablet | 1 tablet twice daily | 60 tablets | $1,931.64 |
| **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** | | | | |
| **Efavirenz** | | | | |
| • Sustiva | 600 mg tablet | 1 tablet daily | 30 tablets | $1,010.13 |
| **Etravirine** | | | | |
| • Intelence | 200 mg tablet | 1 tablet twice daily | 60 tablets | $1,308.06 |
| **Nevirapine** | | | | |
| • Generic | 200 mg tablet | 1 tablet twice daily | 60 tablets | $648.19 |
| • Viramune | 200 mg tablet | 1 tablet twice daily | 60 tablets | $912.86 |
| • Viramune XR | 400 mg tablet | 1 tablet daily | 30 tablets | $846.66 |
| **Rilpivirine** | | | | |
| • Edurant | 25 mg tablet | 1 tablet daily | 30 tablets | $1,075.15 |
| **Protease Inhibitors (PIs)** | | | | |
| **Atazanavir** | | | | |
| • Reyataz | 200 mg capsule | 2 capsules daily | 60 capsules | $1,656.52 |
| • Reyataz | 300 mg capsule[d] | 1 capsule daily | 30 capsules | $1,640.86 |
| **Atazanavir/Cobicistat** | | | | |
| • Evotaz | 300/150 mg tablet | 1 tablet daily | 30 tablets | $1,817.51 |
| **Darunavir** | | | | |
| • Prezista | 600 mg tablet[e] | 1 tablet twice daily | 60 tablets | $1,629.06 |
| • Prezista | 800 mg tablet[d] | 1 tablet daily | 30 tablets | $1,629.06 |
| • Prezista | 100 mg/mL suspension[e] | 8 mL daily<br>6 mL twice daily | 240 mL<br>360 mL | $1,086.05<br>$1,629.07 |
| **Darunavir/Cobicistat** | | | | |
| • Prezcobix | 800/150 mg tablet | 1 tablet daily | 30 tablets | $1,862.12 |
| **Lopinavir/Ritonavir** | | | | |
| • Kaletra | 200/50 mg tablet | 2 tablets twice daily or 4 tablets once daily | 120 tablets | $1,106.29 |
| • Kaletra | 80/20 mg per mL solution | 5 mL twice daily | 300 mL | $1,037.14 |
| **Tipranavir** | | | | |
| • Aptivus | 250 mg capsule[e] | 2 capsules twice daily | 120 capsules | $1,685.59 |



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**Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 4)**

| ARV Drug (Generic and Brand Names) | Strength Formulation | Dosing | Tablets, Capsules, or mLs per Month[a] | AWP[b] (Monthly) |
|---|---|---|---|---|
| **Integrase Strand Transfer Inhibitors (INSTIs)** | | | | |
| **Dolutegravir** • Tivicay | 50 mg tablet | 1 tablet once daily | 30 tablets | $1,707.26 |
| • Tivicay | 50 mg tablet | 1 tablet twice daily | 60 tablets | $3,414.52 |
| **Elvitegravir** • Vitekta | 85 mg tablet | 1 tablet daily | 30 tablets | $1,445.34 |
| • Vitekta | 150 mg tablet | 1 tablet daily | 30 tablets | $1,445.34 |
| **Raltegravir** • Isentress | 400 mg tablet | 1 tablet twice daily | 60 tablets | $1,545.07 |
| **Fusion Inhibitor** | | | | |
| **Enfuviritide** • Fuzeon | 90 mg injection kit | 1 injection twice daily | 60 doses (1 kit) | $4,097.78 |
| **CCR5 Antagonist** | | | | |
| **Maraviroc** • Selzentry | 150 mg tablet | 1 tablet twice daily | 60 tablets | $1,296.77 |
| • Selzentry | 300 mg tablet | 1 tablet twice daily | 60 tablets | $1,296.77 |
| • Selzentry | 300 mg tablet | 2 tablets twice daily | 120 tablets | $2,593.54 |
| **Co-Formulated Combination Products as Single Tablet Regimens** | | | | |
| **Dolutegravir/Abacavir/Lamivudine** • Triumeq | 50/600/300 mg tablet | 1 tablet daily | 30 tablets | $2,889.22 |
| **Efavirenz/Tenofovir Disoproxil Fumarate/Emtricitabine** • Atripla | 600/300/200 mg tablet | 1 tablet daily | 30 tablets | $2,869.86 |
| **Elvitegravir/Cobicistat/Tenofovir Alafenamide/Emtricitabine** • Genvoya | 150/150/10/200 mg tablet | 1 tablet daily | 30 tablets | $3,093.19 |
| **Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/ Emtricitabine** • Stribild | 150/150/300/200 mg tablet | 1 tablet daily | 30 tablets | $3,244.76 |
| **Rilpivirine/Tenofovir Alafenamide/Emtricitabine** • Odefsey | 25/25/200 mg tablet | 1 tablet daily | 30 tablets | $2,815.04 |
| **Rilpivirine/Tenofovir Disoproxil Fumarate/Emtricitabine** • Complera | 25/300/200 mg tablet | 1 tablet daily | 30 tablets | $2,815.04 |
| **Pharmacokinetic Enhancers (Boosters)** | | | | |
| **Cobicistat** • Tybost | 150 mg tablet | 1 tablet daily | 30 tablets | $230.90 |
| **Ritonavir:** Total daily dose depends on the dose of the concomitant PI (100 mg once or twice daily, or 200 mg twice daily) • Norvir | 100 mg tablet | 1 tablet once daily | 30 tablets | $308.60 |
| | 80 mg/mL solution | 100 mg daily | 37.5 mL (of a 240 mL bottle) | $270.04 |



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**Table 16. Monthly Average Wholesale Price[b] of Commonly Used[c] Antiretroviral Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 4)**

| ARV Drug (Generic and Brand Names) | Strength Formulation | Dosing | Tablets, Capsules, or mLs per Month[a] | AWP[b] (Monthly) |
|---|---|---|---|---|

[a] Represents 30 days or as specified.

[b] AWP = average wholesale price. Note that the AWP may not represent the pharmacy acquisition price or the price paid by consumers.

Source: http://micromedexsolutions.com. Accessed April 2016.

[c] The following less commonly used ARV drugs are not included in this table: delavirdine, didanosine, fosamprenavir, indinavir, nelfinavir, saquinavir, and stavudine.

[d] Should be used in combination with ritonavir or cobicistat. Please refer to Appendix B, Table 3 for ritonavir doses.

[e] Should be used in combination with ritonavir. Please refer to Appendix B, Table 3 for ritonavir doses.

**Key to Abbreviations:** ARV = antiretroviral; EC = enteric coated; XR = extended release



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**Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 1 of 2)**

Pharmacokinetic interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (eg, transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

**Note:** Ellipses ( … ) indicate that there are no clinically relevant interactions by these mechanisms.

| ARV Drugs by Drug Class | Mechanisms That May Affect or Be Affected by Oral Absorption of ARV Drugs | | | Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs | | | | Other Mechanisms of Drug Interactions |
|---|---|---|---|---|---|---|---|---|
| | Increasing Gastric pH | Cationic Chelation | P-glycoprotein | CYP Substrate | CYP Inhibitor | CYP Inducer | UGT1A1 | |
| **Integrase Strand Transfer Inhibitors (INSTIs)** | | | | | | | | |
| **Dolutegravir (DTG)** | … | Concentration decreased by products containing polyvalent cations (eg, Ca, Mg, Al, Fe, Zn) | Substrate | 3A4 (small contribution) | … | … | Substrate | Inhibitor of renal transporters OCT2 and MATE |
| **Elvitegravir (EVG)** | … | | … | 3A4 | … | 2C9 | Substrate | … |
| **Raltegravir (RAL)** | … | | … | … | … | … | Substrate | … |
| **Pharmacokinetic (PK) Enhancers (Boosters)** | | | | | | | | |
| **Cobicistat (COBI)** | … | … | Inhibitor | 3A4 | 3A4, 2D6 | … | … | … |
| **Ritonavir (RTV)** | … | … | Substrate, inhibitor | 3A4, 2D6 | 3A4, 2D6 (lesser extent) | 1A2, 2C8, 2C9, 2C19 | Inducer | … |
| **Protease Inhibitors (PIs)** **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions. | | | | | | | | |
| **Atazanavir (ATV)** | Concentration decreased | … | Substrate, inducer, inhibitor | 3A4 | 3A4, 2C8 (weak) | … | Inhibitor | OATP inhibitor |
| **Darunavir (DRV)** | … | … | Substrate | 3A4 | 3A4 | 2C9 | … | OATP inhibitor |



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**Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 2 of 2)**

| ARV Drugs by Drug Class | Mechanisms That May Affect or be Affected by Oral Absorption of ARV Drugs | | | Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs | | | | Other Mechanisms of Drug Interactions |
|---|---|---|---|---|---|---|---|---|
| | Increasing Gastric pH | Cationic Chelation | P-glycoprotein | CYP Substrate | CYP Inhibitor | CYP Inducer | UGT1A1 | |
| **Protease Inhibitors (PIs)**, continued<br>**Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions. | | | | | | | | |
| **Fosamprenavir (FPV)** | Concentration decreased by H2 antagonist | … | Substrate, inhibitor | 3A4 | 3A4 | 3A4 (weak) | … | … |
| **Lopinavir (LPV)** | … | … | Substrate | 3A4 | 3A4 | … | … | OATP inhibitor |
| **Saquinavir (SQV)** | … | … | Substrate, inhibitor | 3A4 | 3A4 | … | … | OATP inhibitor |
| **Tipranavir (TPV)** | … | … | Substrate, inducer | 3A4 | 2D6 | 3A4, 1A2, 2C19 | … | OATP inhibitor |
| **Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** | | | | | | | | |
| **Efavirenz (EFV)** | … | … | … | 2B6 (primary), 2A6, 3A4 | 2C9, 2C19, 3A4 | 3A4, 2B6 | … | … |
| **Etravirine (ETR)** | … | … | Inducer | 3A4, 2C9, 2C19 | 2C9, 2C19 | 3A4 | … | … |
| **Nevirapine (NVP)** | … | … | … | 3A4, 2B6 | … | 3A4, 2B6 | … | … |
| **Rilpivirine (RPV)** | Concentration decreased | … | … | 3A4 | … | … | … | … |
| **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** | | | | | | | | |
| **Abacavir (ABC)** | … | … | … | … | … | … | Substrate | Alcohol dehydrogenase substrate |
| **Emtricitabine (FTC)** | … | … | … | … | … | … | … | … |
| **Lamivudine (3TC)** | … | … | … | … | … | … | … | … |
| **Tenofovir alafenamide (TAF)** | … | … | Substrate | … | … | … | … | OATP substrate |
| **Tenofovir disoproxil fumarate (TDF)** | … | … | Substrate | … | … | … | … | Competition of active renal tubular secretion |
| **Zidovudine (ZDV)** | … | … | … | … | … | … | … | Glucuronidation |
| **CCR5 Antagonist** | | | | | | | | |
| **Maraviroc (MVC)** | … | … | Substrate | 3A4 | … | … | … | … |
| **Fusion Inhibitor** | | | | | | | | |
| **Enfuvirtide (T20)** | … | … | … | … | … | … | … | … |

**Key to Abbreviations:** Al = aluminium; ARV = antiretroviral; Ca = calcium; CYP = cytochrome P; Fe = iron; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; OATP = organic anion-transporting polypeptide; OCT2 = organic cation transporter 2; UGT1A1 = uridine diphosphate glucuronosyltransferase; Zn = zinc



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**Table 18. Drugs That Should Not Be Used With Selected Antiretroviral Agents Due to Proven or Predicted Pharmacokinetic Interactions (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)**

This table only lists drugs that should not be coadministered at any dose, regardless of RTV or COBI boosting (unless stated otherwise). See Tables 19 and 20 for more detailed pharmacokinetic (PK) interaction data.

| ARV Agents[a,b] | Cardiac Agents | Lipid-Lowering Agents | Anti-infective Agents | Antiepileptic Agents | Neurologic Agents | Herbs | HCV Agents[c] | Other Agents |
|---|---|---|---|---|---|---|---|---|
| **ATV +/– RTV or COBI** | Dronedarone<br>Eplerenone<br>Ivabradine<br>Ranolazine | Lovastatin<br>Simvastatin | Rifampin<br>Rifapentine | **ATV/c only:**<br>Carbamazepine<br>Phenobarbital<br>Phenytoin | Lurasidone<br>Midazolam[e]<br>Pimozide<br>Triazolam | St. John's wort | Elbasvir/ Grazoprevir<br>Simeprevir | Alfuzosin<br>Cisapride[f]<br>Ergot derivatives<br>Flibanserin<br>Irinotecan<br>Salmeterol<br>Sildenafil for PAH |
| **DRV/c or DRV/r** | Dronedarone<br>Eplerenone<br>Ivabradine<br>Ranolazine | Lovastatin<br>Simvastatin | Rifampin<br>Rifapentine | **DRV/c only:**<br>Carbamazepine<br>Phenobarbital<br>Phenytoin | Lurasidone<br>Midazolam[e]<br>Pimozide<br>Triazolam | St. John's wort | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | Alfuzosin<br>Cisapride[e]<br>Ergot derivatives<br>Flibanserin<br>Salmeterol<br>Sildenafil for PAH |
| **FPV +/– RTV** | Dronedarone<br>Eplerenone<br>Flecainide<br>Ivabradine<br>Propafenone<br>Ranolazine | Lovastatin<br>Simvastatin | Rifampin<br>Rifapentine | None | Lurasidone<br>Midazolam[e]<br>Pimozide<br>Triazolam | St. John's wort | Dasabuvir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | Alfuzosin<br>Cisapride[e]<br>Ergot derivatives<br>Flibanserin<br>Salmeterol<br>Sildenafil for PAH |
| **LPV/r** | Dronedarone<br>Eplerenone<br>Ivabradine<br>Ranolazine | Lovastatin<br>Simvastatin | Rifampin[f]<br>Rifapentine | None | Lurasidone<br>Midazolam[e]<br>Pimozide<br>Triazolam | St. John's wort | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | Alfuzosin<br>Cisapride[e]<br>Ergot derivatives<br>Flibanserin<br>Salmeterol<br>Sildenafil for PAH |
| **SQV/r** | Amiodarone<br>Disopyramide<br>Dofetilide<br>Dronedarone<br>Eplerenone<br>Flecainide<br>Ivabradine<br>Lidocaine<br>Propafenone<br>Quinidine<br>Ranolazine | Lovastatin<br>Simvastatin | Clarithromycin<br>Dapsone<br>Erythromycin<br>Pentamidine (parenteral)<br>Rifampin[f]<br>Rifapentine<br>Quinine | None | Clozapine<br>Haloperidol<br>Lurasidone<br>Midazolam[e]<br>Phenothiazines[g]<br>Pimozide<br>Trazodone<br>Triazolam<br>Ziprasidone | ments<br>St. John's wort<br>Garlic supple- | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | Alfuzosin<br>Cisapride[f]<br>Ergot derivatives<br>Flibanserin<br>Tacrolimus<br>Salmeterol<br>Sildenafil for PAH |
| **TPV/r** | Amiodarone<br>Dronedarone<br>Eplerenone<br>Flecainide<br>Ivabradine<br>Propafenone<br>Quinidine<br>Ranolazine | Lovastatin<br>Simvastatin | Rifampin<br>Rifapentine | None | Lurasidone<br>Midazolam[d]<br>Pimozide<br>Triazolam | St. John's wort | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ledipasvir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir<br>Sofosbuvir | Alfuzosin<br>Cisapride[e]<br>Ergot derivatives<br>Flibanserin<br>Salmeterol<br>Sildenafil for PAH |
| **EFV** | None | None | None | None | None | St. John's wort | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | None |



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**Table 18. Drugs That Should Not Be Used With Selected Antiretroviral Agents Due to Proven or Predicted Pharmacokinetic Interactions (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)**

This table only lists drugs that should not be coadministered at any dose, regardless of RTV or COBI boosting (unless stated otherwise). See Tables 19 and 20 for more detailed pharmacokinetic (PK) interaction data.

| ARV Agents[a,b] | Cardiac Agents | Lipid-Lowering Agents | Anti-infective Agents | Antiepileptic Agents | Neurologic Agents | Herbs | HCV Agents[c] | Other Agents |
|---|---|---|---|---|---|---|---|---|
| **ETR** | None | None | Rifampin<br>Rifapentine | Carbamazepine<br>Phenobarbital<br>Phenytoin | None | St John's wort | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | Clopidogrel |
| **NVP** | None | None | Rifapentine | None | None | St. John's wort | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | Ketoconazole |
| **RPV** | None | None | Rifampin<br>Rifapentine | Carbamazepine<br>Oxcarbazepine<br>Phenobarbital<br>Phenytoin | None | St. John's wort | Dasabuvir<br>Ombitasvir<br>Paritaprevir | Proton pump inhibitors |
| **MVC** | None | None | Rifapentine | None | None | St. John's wort | Dasabuvir<br>Ombitasvir<br>Paritaprevir | None |
| **DTG** | Dofetilide | None | Rifapentine | None | None | St. John's wort | None | None |
| **EVG/c**<br><br>**For EVG + PI/r, refer to agents listed for the selected PI** | Eplerenone<br>Ivabradine<br>Ranolazine | Lovastatin<br>Simvastatin | Rifampin<br>Rifapentine | Carbamazepine<br>Phenobarbital<br>Phenytoin | Lurasidone<br>Pimozide<br>Midazolam[d]<br>Triazolam | St. John's wort | Dasabuvir<br>Elbasvir/ Grazoprevir<br>Ledipasvir<br>Ombitasvir<br>Paritaprevir<br>Simeprevir | Alfuzosin<br>Cisapride[e]<br>Ergot derivatives<br>Flibanserin<br>Salmeterol<br>Sildenafil for PAH |
| **RAL** | None | None | None | None | None | None | None | None |
| **TAF** | None | None | Rifabutin<br>Rifampin<br>Rifapentine | None | None | St. John's wort | None | None |

[a] DLV, IDV, NFV, RTV (as sole PI), T-20, and NRTIs other than TAF are not included in this table. Refer to the appropriate FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

[b] Certain listed drugs are contraindicated on the basis of theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

[c] HCV agents listed include only those that are commercially available at the publication of these guidelines.

[d] Use of oral midazolam is contraindicated. Single-dose parenteral midazolam can be used with caution and can be given in a monitored situation for procedural sedation.

[e] The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

[f] In healthy volunteer studies, a high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect; therefore, these dosing strategies should not be used when alternatives exist.

[g] Phenothiazines include chlorpromazine, fluphenazine, mesoridazine, perphenazine, prochlorperazine, promethazine, and thioridazine.

Suggested alternatives to:

- **Lovastatin, simvastatin:** Fluvastatin, pitavastatin, and pravastatin (except for pravastatin with DRV/r) have the least potential for drug-drug interactions (see Table 19a). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
- **Rifampin:** Rifabutin (with dosage adjustment, see Tables 19a and 19b)



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• **Midazolam, triazolam:** Temazepam, lorazepam, oxazepam

• **Sildenafil for PAH:** Selexipag

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; CYP = cytochrome P; DLV = delavirdine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HCV = hepatitis C virus; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NVP = nevirapine; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TB = tuberculosis; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TPV/r = tipranavir/ritonavir



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## Table 19a. Drug Interactions Between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 15)

This table provides known or predicted information regarding PK interactions between PIs and non-ARV drugs. When information is available, interactions for specific PK-boosted (with either RTV or COBI) and unboosted PIs are listed separately. The term "All PIs" refers to both unboosted PIs and PIs boosted with either RTV or COBI. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a, and 20b.

**Note:** NFV and IDV are **not** included in this table. Please refer to the FDA product labels for NFV and IDV for information regarding drug interactions with these PIs.

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Acid Reducers** | | | |
| **Antacids** | ATV, ATV/c, ATV/r | When given simultaneously, ↓ ATV expected | Give ATV at least 2 hours before or 1 to 2 hours after antacids or buffered medications. |
| | FPV | APV AUC ↓ 18%; ↔ in APV $C_{min}$ | Give FPV simultaneously with (or at least 2 hours before or 1 hour after) antacids. |
| | TPV/r | TPV AUC ↓ 27% | Give TPV at least 2 hours before or 1 hour after antacids. |
| **H2 Receptor Antagonists** | ATV (unboosted) | ↓ ATV | H2 receptor antagonist single dose should not exceed a dose equivalent to famotidine 20 mg and the total daily dose should not exceed a dose equivalent to famotidine 20 mg BID in ART-naive patients.<br>Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist. |
| | ATV/c, ATV/r | ↓ ATV | H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients.<br>Give ATV 300 mg plus COBI 150 mg or RTV 100 mg simultaneously with and/or ≥10 hours after the dose of H2 receptor antagonist.<br>If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg plus COBI 150 mg or RTV 100 mg. |
| | DRV/c, DRV/r, LPV/r | No significant effect shown or expected | No dosage adjustment necessary. |
| | FPV (unboosted) | APV AUC ↓ 30%; no significant change in APV $C_{min}$ | If concomitant use is necessary, give FPV at least 2 hours before H2 receptor antagonist. Consider boosting FPV with RTV. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **PPIs** | ATV (unboosted) | ↓ ATV | **PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, RTV or COBI boosting, or alternative PIs. |
| | ATV/c, ATV/r | ↓ ATV | PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r.<br>**PPIs are not recommended in PI-experienced patients.** |
| | DRV/c | No significant effect expected | No dosage adjustment necessary. |
| | DRV/r | omeprazole AUC ↓ 42% | No dosage adjustment necessary. |
| | FPV, FPV/r, LPV/r | No significant effect | No dosage adjustment necessary. |
| | SQV/r | SQV AUC ↑ 82% | Monitor for SQV toxicities. |
| | TPV/r | ↓ omeprazole | May need to increase omeprazole dose. |
| **Anticoagulants and Antiplatelets** | | | |
| **Apixaban** | All PIs | ↑ apixaban expected | **Avoid concomitant use.** |
| **Dabigatran** | All RTV-boosted PIs, ATV/c, DRV/c | ↑ dabigatran possible | No dosage adjustment if CrCl >50 mL/min.<br>**Avoid coadministration if CrCl <50 mL/min.** |
| **Edoxaban** | All PIs | ↑ edoxaban | Avoid concomitant use. |
| **Rivaroxaban** | All PIs | ↑ rivaroxaban | **Avoid concomitant use.** |
| **Ticagrelor** | All PIs | ↑ ticagrelor expected | **Avoid concomitant use.** |
| **Vorapaxar** | All PIs | ↑ vorapaxar expected | **Avoid concomitant use.** |
| **Warfarin** | PI/r | ↓ warfarin possible | Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly. |
| | ATV/c, DRV/c | No data | Monitor INR closely when stopping or starting PI/c and adjust warfarin dose accordingly.<br>If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin. |
| **Anticonvulsants** | | | |
| **Carbamazepine** | ATV, FPV (unboosted) | May ↓ PI levels substantially | **Do not coadminister.** Consider alternative anticonvulsant or ATV/r, ATV/c, or FPV/r. |
| | ATV/c, DRV/c | ↓ cobicistat expected<br>↓ PI levels expected | **Contraindicated. Do not coadminister.** |
| | ATV/r, FPV/r, LPV/r, SQV/r, TPV/r | ↑ carbamazepine possible<br>TPV/r ↑ carbamazepine AUC 26%<br>May ↓ PI levels substantially | Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r or FPV/r once daily.** |
| | DRV/r | carbamazepine AUC ↑ 45%<br>DRV: no significant change | Monitor anticonvulsant level and adjust dose accordingly. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Anticonvulsants**, continued | | | |
| **Ethosuximide** | All PIs | ↑ ethosuximide possible | Clinically monitor for ethosuxamide toxicities. |
| **Lamotrigine** | ATV (unboosted) | lamotrigine: no effect | No dose adjustment necessary. |
| | ATV/r | lamotrigine AUC ↓ 32% | A dose increase of lamotrigine may be needed; consider monitoring lamotrigine concentration or consider alternative anticonvulsant. |
| | LPV/r | lamotrigine AUC ↓ 50%<br>LPV: no significant change | |
| | PI/r (other than ATV/r or LPV/r) | ↓ lamotrigine possible | |
| | ATV/c, DRV/c | No data | Monitor lamotrigine concentration or consider alternative anticonvulsant. |
| **Phenobarbital** | ATV/c<br>DRV/c | ↓ cobicistat expected<br>↓ PI levels expected | **Contraindicated. Do not coadminister.** |
| | All unboosted PI or PI/r | May ↓ PI levels substantially | Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.<br>**Do not coadminister with LPV/r or FPV/r once daily, or unboosted ATV or FPV.** |
| **Phenytoin** | ATV, FPV (unboosted) | May ↓ PI levels substantially | **Do not coadminister.** Consider alternative anticonvulsant or either ATV/r or FPV/r. |
| | ATV/r, DRV/r, SQV/r, TPV/r | ↓ phenytoin possible<br>↓ PI possible | Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. |
| | ATV/c, DRV/c | ↓ cobicistat expected<br>↓ PI levels expected | **Contraindicated. Do not coadminister.** |
| | FPV/r | phenytoin AUC ↓ 22%<br>APV AUC ↑ 20% | Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended. |
| | LPV/r | phenytoin AUC ↓ 31%<br>LPV/r AUC ↓ 33% | Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.<br>**Do not coadminister with LPV/r once daily.** |
| **Valproic Acid** | LPV/r | ↓ or ↔ VPA possible<br>LPV AUC ↑ 75% | Monitor VPA levels and virologic response. Monitor for LPV-related toxicities. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antidepressants, Anxiolytics, and Antipsychotics (Also see Sedative/Hypnotics section below.)** | | | |
| **Bupropion** | LPV/r | bupropion AUC ↓ 57% | Titrate bupropion dose based on clinical response. |
| | TPV/r | bupropion AUC ↓ 46% | |
| **Buspirone** | All PIs | ↑ buspirone expected | Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response. |
| **Fluvoxamine** | All PIs | ↑ or ↓ PI possible | Consider alternative therapeutic agent. |
| **Other Selective Serotonin Reuptake Inhibitors (SSRIs)** (eg, citalopram, escitalopram, fluoxetine, paroxetine, sertraline) | RTV | escitalopram ↔ | Titrate SSRI dose based on clinical response. |
| | DRV/r | paroxetine AUC ↓ 39%<br>sertraline AUC ↓ 49% | |
| | FPV/r | paroxetine AUC ↓ 55% | |
| | ATV/r, LPV/r, SQV/r, TPV/r | No data | |
| | ATV/c, DRV/c | Effects unknown | Titrate SSRI dose using the lowest available initial or maintenance dose. |
| **Quetiapine** | All PIs | ↑ quetiapine expected | Starting quetiapine in a patient receiving a PI:<br>• Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects.<br>Starting a PI in a patient receiving a stable dose of quetiapine:<br>• Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects. |
| **Other Antipsychotics** (eg, perphenazine, risperidone, thioridazine) | ATV/c DRV/c, All PI/r | ↑ antipsychotic possible | Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities. |
| **Trazodone** | All PIs except SQV/r | RTV 200 mg BID (for 2 days) ↑ trazodone AUC 240% | Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects. |
| | SQV/r | ↑ trazodone expected | **Contraindicated. Do not coadminister.** |
| **Tricyclic Antidepressants** Amitriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline | All PI/r, ATV/c, DRV/c | ↑ TCA expected | Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antifungals** | | | |
| **Fluconazole** | ATV/c, ATV/r | No significant effect observed or expected | No dosage adjustment necessary. |
| | SQV/r | No data with RTV boosting | No dosage adjustment necessary. |
| | TPV/r | TPV AUC ↑ 50% | Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative ARV. |
| **Isavuconazole** | LPV/r | Isavuconazole AUC ↑ 96%<br>LPV AUC ↓ 27% | If coadministered, consider monitoring isavuconazole concentrations and assessing virologic response. |
| | All PIs except LPV/r | ↑ isavuconazole possible<br>↑ or ↓ PI possible | If coadministered, consider monitoring isavuconazole concentrations. Monitor for PI toxicity and virologic response. |
| **Itraconazole** | All PIs | ↑ itraconazole possible<br>↑ PI possible | Consider monitoring itraconazole level to guide dosage adjustments. Doses >200 mg/day are not recommended with PI/r, ATV/c, or DRV/c unless dosing is guided by itraconazole levels. |
| **Posaconazole** | ATV/c | ↑ ATV possible | Monitor for adverse effects of ATV. |
| | ATV/r | ATV AUC ↑ 146% | |
| | ATV | ATV AUC ↑ 268% | |
| | FPV | With FPV 700 mg BID (without RTV): posaconazole AUC ↓ 23%, APV AUC similar to that with FPV 1400 mg BID<br>With FPV 1400 mg BID: ↑ APV expected | If coadministered, monitor posaconazole concentrations. |
| | DRV/c, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r | ↑ PI possible<br>↑ posaconazole possible | If coadministered, consider monitoring posaconazole concentrations. Monitor for PI adverse effects. |
| **Voriconazole** | ATV, FPV (unboosted) | ↑ voriconazole possible<br>↑ PI possible | Monitor for toxicities. |
| | All PI/r | RTV 400 mg BID ↓ voriconazole AUC 82%<br>RTV 100 mg BID ↓ voriconazole AUC 39% | **Do not coadminister voriconazole and RTV or COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentration and adjust dose accordingly |
| | ATV/c, DRV/c | Effects unknown | |
| **Antimalarials** | | | |
| **Artemether/ Lumefantrine** | DRV/r | artemether AUC ↓ 16%<br>DHA[a] AUC ↓ 18%<br>lumefantrine AUC ↑ 2.5-fold | Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity. |
| | DRV/c | ↑ lumefantrine expected<br>Effect on artemether unknown | |
| | LPV/r | artemether AUC ↓ 40%<br>DHA AUC ↓ 17%<br>lumefantrine AUC ↑ 470% | |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antimalarials, continued** | | | |
| **Artesunate/ Mefloquine** | LPV/r | dihydroartemisinin AUC ↓ 49%<br>mefloquine AUC ↓ 28%<br>LPV ↔ | Clinical significance unknown. If used, monitor closely for antimalarial efficacy. |
| **Atovaquone/ Proguanil** | ATV/r, LPV/r | ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41%<br>LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38% | No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible. |
| **Mefloquine** | RTV | With RTV 200 mg BID: RTV AUC ↓ 31%, $C_{min}$ ↓ 43%; ↔ mefloquine | Use with caution. Effect on exposure of RTV-boosted PIs is unknown. |
| **Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and non-tuberculosis mycobacterial infections)** | | | |
| **Bedaquiline** | All PI/r, ATV/c, DRV/c | With LPV/r: bedaquiline AUC ↑ 1.9 fold<br>With other PI/r, ATV/c, or DRV/c: ↑ bedaquiline possible | Clinical significance unknown. Use with caution if benefit outweighs the risk and monitor for QTc prolongation and liver function tests. |
| **Clarithromycin** | ATV (unboosted) | clarithromycin AUC ↑ 94% | May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (eg, azithromycin). |
| | All PI/r, ATV/c, DRV/c | ↑ clarithromycin expected | Consider alternative macrolide (eg, azithromycin) |
| | | DRV/r ↑ clarithromycin AUC 57%<br>FPV/r ↑ clarithromycin possible<br>LPV/r ↑ clarithromycin expected<br>RTV 500 mg BID ↑ clarithromycin 77%<br>SQV unboosted ↑ clarithromycin 45%<br>TPV/r ↑ clarithromycin 19%<br>clarithromycin ↑ unboosted SQV 177%<br>clarithromycin ↑ TPV 66% | Monitor for clarithromycin-related toxicities or consider alternative macrolide (eg, azithromycin).<br>Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min.<br>Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min. |
| | FPV | APV AUC ↑ 18% | No dosage adjustment necessary. |
| **Rifabutin** | ATV (unboosted) | ↑ rifabutin AUC expected | Rifabutin 150 mg daily or 300 mg three times a week |
| | FPV (unboosted) | No data | Consider alternative ARV. |
| | ATV/c, DRV/c | ↑ rifabutin expected | Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring.<br>PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants. |
| | ATV/r | Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg once daily) with ATV/r, rifabutin AUC ↑ 110% and metabolite AUC ↑ 2101% | |
| | DRV/r | Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg every other day) with DRV/r, rifabutin AUC ↔ and metabolite AUC ↑ 881% | |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and non-tuberculosis mycobacterial infections), continued** | | | |
| **Rifabutin,** continued | FPV/r | Compared with rifabutin (300 mg once daily) alone, rifabutin (150 mg every other day) with FPV/r, rifabutin and metabolite AUC ↑ 64%. | Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring.<br>PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants. |
| | LPV/r | Compared with rifabutin (300 mg daily) alone, rifabutin (150 mg once daily) with LPV/r, rifabutin and metabolite AUC ↑ 473%. | |
| | SQV/r | ↑ rifabutin with unboosted SQV | |
| | TPV/r | rifabutin and metabolite AUC ↑ 333% | |
| **Rifampin** | All PIs | ↓ PI concentration by >75% | **Do not coadminister rifampin and PIs.** Additional RTV does not overcome this interaction and may increase hepatotoxicity. Additional COBI is not recommended. Consider rifabutin if a rifamycin is indicated. |
| **Rifapentine** | All PIs | ↓ PI expected | **Do not coadminister.** |
| **Antipneumocystis and Antitoxoplasmosis Drug** | | | |
| **Atovaquone** | ATV/r | Atovaquone ↔ | No dosage adjustment necessary. |
| **Cardiac Medications** | | | |
| **Amiodarone** | SQV/r, TPV/r | ↑ both amiodarone and PI possible | **Do not coadminister.** |
| | All PIs (except SQV/r, TPV/r) | ↑ both amiodarone and PI possible | Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring. |
| **Antiarrhythmics** (eg, dofetilide, dronedarone, flecainide, lidocaine, propafenone, quinidine) | SQV/r | ↑ antiarrhythmic possible | **Do not coadminister.** |
| | All PIs | ↑ antiarrhythmic possible | Use with caution. **Refer to Table 18 for contraindicated combinations.** |
| **Beta-blockers** (eg, metoprolol, timolol) | All PIs | ↑ beta-blockers possible | May need to decrease beta-blocker dose; adjust dose based on clinical response.<br>Consider using beta-blockers that are not metabolized by CYP450 enzymes (eg, atenolol, labetalol, nadolol, sotalol). |
| **Bosentan** | All PIs | LPV/r ↑ bosentan 48-fold (day 4) and 5-fold (day 10)<br>↓ ATV expected | **Do not coadminister bosentan and unboosted ATV.**<br>In Patients on a PI (Other than Unboosted ATV) >10 Days:<br>• Start bosentan at 62.5 mg once daily or every other day.<br>In Patients on Bosentan who Require a PI (Other than Unboosted ATV):<br>• Stop bosentan ≥36 hours before PI initiation and 10 days after PI initiation restart bosentan at 62.5 mg once daily or every other day.<br>When switching between COBI and RTV:<br>• Maintain same bosentan dose. |



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| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Cardiac Medications, continued** | | | |
| **Calcium Channel Blockers (CCBs)** (except diltiazem) | All PIs | ↑ dihydropyridine possible<br>↑ verapamil possible | Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB used with ATV and SQV. |
| **Digoxin** | PI/r, ATV/c, or DRV/c | RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43%<br>SQV/r ↑ digoxin AUC 49%<br>DRV/r ↑ digoxin AUC 36%<br>COBI ↑ digoxin $C_{max}$ 41%, AUC ↔ | Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose. |
| **Diltiazem** | ATV/c, ATV/r, ATV | Unboosted ATV ↑ diltiazem AUC 125%<br>Greater ↑ likely with ATV/c or ATV/r | Decrease diltiazem dose by 50%. ECG monitoring is recommended. |
| | DRV/c, DRV/r, FPV/r, FPV, LPV/r, SQV/r, TPV/r | ↑ diltiazem possible | Use with caution. Adjust diltiazem according to clinical response and toxicities. |
| **Eplerenone** | All PIs | ↑ eplerenone expected | **Contraindicated. Do not coadminister.** |
| **Ivabradine** | All PIs | ↑ ivabradine expected | **Contraindicated. Do not coadminister.** |
| **Cortocosteroids** | | | |
| **Beclomethasone** Inhaled | DRV/r | RTV 100 mg BID ↑ 17-BMP AUC 2-fold and ↑ $C_{max}$ 1.6-fold<br>(DRV 600 mg + RTV 100 mg) BID ↓ 17-BMP AUC 11% and ↓ $C_{max}$ 19% | No dosage adjustment necessary.<br>Significant interaction between beclomethasone (inhaled or intranasal) and other PI/r, ATV/c, or DRV/c is not expected. |
| **Budesonide** Systemic | All PIs | ↓ PI levels possible<br>↑ glucocorticoids | Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.** |
| **Budesonide, Fluticasone, Mometasone** Inhaled or Intranasal | All PI/r, ATV/c, DRV/c | ↑ glucocorticoids possible<br>RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ $C_{max}$ 25-fold | Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Consider alternative corticosteroid (eg, beclomethasone). |
| **Dexamethasone** Systemic | All PIs | ↓ PI levels possible | Use systemic dexamethasone with caution. Consider alternative corticosteroid for long-term use. |
| **Prednisone** | LPV/r | ↑ prednisolone AUC 31% | Use with caution. Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.** |
| | All PIs | ↑ prednisolone possible | |
| **Methyl-prednisolone, Prednisolone, Triamcinolone** (local injections, including intra-articular, epidural, intra-orbital) | All PI/r, ATV/c, DRV/c | ↑ glucocorticoids expected | **Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 9 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Hepatitis C Direct-Acting Antiviral Agents** | | | |
| **Daclatasvir** | ATV/c or ATV/r SQV/r | ↑ daclatasvir | Decrease daclatasvir dose to 30 mg once daily. |
| | DRV/c DRV/r LPV/r ATV (unboosted) FPV/r or FPV (unboosted) | ↔ daclatasvir | No dose adjustment necessary. |
| | TPV/r | No data | No dosing recommendations at this time. |
| **Dasabuvir + Paritaprevir/ Ombitasvir/RTV** | ATV | ATV ↔ | ATV 300 mg alone, **without COBI or additional RTV**, should be given in the morning with dasabuvir + paritaprevir/ ombitasvir/RTV. |
| | DRV | DRV $C_{min}$ ↓ 43% to 48% | **Do not coadminister.** |
| | LPV/r | paritaprevir AUC ↑ 117% | **Do not coadminister.** |
| | ATV/c, DRV/c, FPV, SQV, TPV | No data | **Do not coadminister.** |
| **Elbasvir/ grazoprevir** | ATV/r | elbasvir AUC ↑ 4.8 fold<br>grazoprevir AUC ↑ 10.6 fold<br>ATV ↔ by elbasvir<br>ATV AUC ↑ 43% by grazoprevir | **Contraindicated. Do not coadminister.**<br>May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition |
| | DRV/r | elbasvir AUC ↑ 66%<br>grazoprevir AUC ↑ 7.5 fold<br>DRV ↔ | |
| | LPV/r | elbasvir AUC ↑ 3.7 fold<br>grazoprevir AUC ↑ 12.9 fold<br>LPV ↔ | |
| | ATV, ATV/c, DRV/c, SQV/r, TPV/r | ↑ grazoprevir expected | |
| | FPV/r FPV (unboosted) | No data | No dosing recommendations at this time. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 10 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Hepatitis C Direct-Acting Antiviral Agents, continued** | | | |
| **Ledipasvir/ Sofosbuvir** | ATV/r | ATV AUC ↑ 33%<br>ledipasvir AUC ↑ 113%<br>sofosbuvir: no significant effect | No dosage adjustment necessary.<br>Coadministration of ledipasvir/sofosbuvir with TDF and a PI/r results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions. |
| | DRV/r | DRV: no significant effect expected<br>ledipasvir/sofosbuvir: no significant effect | |
| | ATV/c, DRV/c, FPV, FPV/r, LPV/r, SQV/r | No significant effect expected | |
| | TPV/r | ↓ ledipasvir and sofosbuvir expected | **Do not coadminister.** |
| **Simeprevir** | All PIs | Compared with simeprevir 150 mg alone, simeprevir 50 mg plus DRV/r 800/100 mg daily, simeprevir AUC ↑ 159%<br>RTV 100 mg BID ↑ simeprevir AUC 618% | **Do not coadminister.** |
| **Sofosbuvir** | TPV/r | ↓ sofosbuvir expected | **Do not coadminister.** |
| **Herbal Products** | | | |
| **St. John's Wort** | All PIs | ↓ PI expected | **Do not coadminister.** |
| **Hormonal Contraceptives** | | | |
| **Hormonal Contraceptives (oral)** | ATV (unboosted) | ethinyl estradiol AUC ↑ 48%<br>norethindrone AUC ↑ 110% | Prescribe oral contraceptive that contains no more than 30 mcg of ethinyl estradiol or recommend alternative contraceptive method.<br>Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.[c] |
| | ATV/r | ethinyl estradiol AUC ↓ 19% and $C_{min}$ ↓ 37%<br>norgestimate ↑ 85%<br>norethindrone AUC ↑ 51% and $C_{min}$ ↑ 67% | Oral contraceptive should contain at least 35 mcg of ethinyl estradiol.[b]<br>Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied. |
| | ATV/c, DRV/c | Effects unknown | Consider alternative or additional contraceptive method or alternative ARV drug. |
| | DRV/r, FPV/r, LPV/r, SQV/r, TPV/r | ethinyl estradiol AUC ↓ 37% to 48%<br>norethindrone AUC ↓ 14% to 34%<br>With TPV/r: norethindrone AUC ↔ | Consider alternative or additional contraceptive method or alternative ARV drug. |
| | FPV | With APV: ↑ ethinyl estradiol<br>↑ norethindrone $C_{min}$<br>APV $C_{min}$ ↓ 20% | Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.[c]<br>Oral contraceptives containing progestins other than norethindrone have not been studied. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 11 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Hormonal Contraceptives, continued** | | | |
| **Depot medroxy-progesterone acetate (MPA) injectable** | LPV/r | MPA AUC ↑46%; $C_{min}$ no significant change | Use standard dose. |
| **Etonogestrel-releasing subdermal implant** | LPV/r | etonogestrel AUC ↑ 52% and $C_{min}$ ↑ 34% | Use standard dose. |
| | All other PIs | No data | Consider alternative or additional contraceptive method or alternative ARV drug. |
| **Transdermal ethinyl estradiol/ norelgestromin** | LPV/r | LPV ↔<br>ethinyl estradiol AUC ↓ 45%, norelgestromin AUC ↑ 83% | Use standard dose. |
| | All other PIs | No data | Consider alternative or additional contraceptive method or alternative ARV drug. |
| **HMG-CoA Reductase Inhibitors** | | | |
| **Atorvastatin** | ATV, ATV/c, ATV/r, DRV/c | ↑ atorvastatin possible | Titrate atorvastatin dose carefully and use lowest dose necessary. |
| | DRV/r<br>FPV, FPV/r,<br>SQV/r | DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone<br>FPV +/– RTV ↑ atorvastatin AUC 130% to 153%<br>SQV/r ↑ atorvastatin AUC 79% | Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily. |
| | LPV/r | LPV/r ↑ atorvastatin AUC 488% | Use with caution and use the lowest atorvastatin dose necessary. |
| | TPV/r | ↑ atorvastatin AUC 836% | **Do not coadminister.** |
| **Lovastatin** | All PIs | Significant ↑ lovastatin expected | **Contraindicated. Do not coadminister.** |
| **Pitavastatin** | All PIs | ATV ↑ pitavastatin AUC 31%, $C_{max}$ ↑ 60%<br>ATV: no significant effect<br>DRV/r: no significant effect<br>LPV/r ↓ pitavastatin AUC 20%<br>LPV: no significant effect | No dose adjustment necessary. |
| **Pravastatin** | ATV/c, ATV/r | No data | Use lowest starting dose of pravastatin and monitor for efficacy and adverse effects. |
| | DRV/c, DRV/r | With DRV/r, pravastatin AUC<br>• ↑ 81% following single dose of pravastatin<br>• ↑ 23% at steady state | Use lowest possible starting dose of pravastatin with careful monitoring. |
| | LPV/r | pravastatin AUC ↑ 33% | No dose adjustment necessary. |
| | SQV/r | pravastatin AUC ↓ 47% to 50% | No dose adjustment necessary. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 12 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **HMG-CoA Reductase Inhibitors, continued** | | | |
| **Rosuvastatin** | ATV/c, DRV/c | ↑ rosuvastatin possible | Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities. |
| | ATV/r, LPV/r | ATV/r ↑ rosuvastatin AUC 3-fold and $C_{max}$ ↑7-fold<br>LPV/r ↑ rosuvastatin AUC 108% and $C_{max}$ ↑ 366% | Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily. |
| | DRV/r | rosuvastatin AUC ↑ 48% and $C_{max}$ ↑ 139% | Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities. |
| | FPV +/- RTV | No significant effect on rosuvastatin | No dosage adjustment necessary. |
| | SQV/r | No data available | Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities. |
| | TPV/r | rosuvastatin AUC ↑ 26% and $C_{max}$ ↑ 123% | No dosage adjustment necessary. |
| **Simvastatin** | All PIs | Significant ↑ simvastatin level: SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059% | Contraindicated. Do not coadminister. |
| **Immunosuppressants** | | | |
| **Cyclosporine, Everolimus, Sirolimus, Tacrolimus** | All PIs | ↑ immunosuppressant expected | Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immuno-suppressant and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary. |
| **Narcotics and Treatment for Opioid Dependence** | | | |
| **Buprenorphine sublingual/ buccal/implant** | ATV (unboosted) | buprenorphine AUC ↑ 93%<br>norbuprenorphine[d] AUC ↑ 76%<br>↓ ATV possible | **Do not coadminister buprenorphine with unboosted ATV.** |
| | ATV/r | buprenorphine AUC ↑ 66%<br>norbuprenorphine[d] AUC ↑ 105% | Monitor for sedation and other signs or symptoms of over-medication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. |
| | ATV/c, DRV/c | Effects unknown | Titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Clinical monitoring is recommended. |
| | DRV/r | buprenorphine: no significant effect<br>norbuprenorphine[d] AUC ↑ 46% and $C_{min}$ ↑ 71% | No dosage adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive. |
| | FPV/r | buprenorphine: no significant effect<br>norbuprenorphine[d] AUC ↓ 15% | |
| | LPV/r | No significant effect | |
| | TPV/r | buprenorphine: no significant effect<br>norbuprenorphine[d] AUC, $C_{max}$, and $C_{min}$ ↓ 80%<br>TPV $C_{min}$ ↓ 19% to 40% | Consider monitoring TPV level. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 13 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Narcotics and Treatment for Opioid Dependence, continued** | | | |
| **Fentanyl** | All PIs | ↑ fentanyl possible | Clinical monitoring is recommended, including for potentially fatal respiratory depression. |
| **Methadone** | ATV (unboosted) | No significant effect | No dosage adjustment necessary. |
| | ATV/c, DRV/c | Effects unknown | Titrate methadone dose using the lowest feasible initial dose. Dose adjustment of methadone may be needed. Clinical monitoring is recommended. |
| | FPV (unboosted) | No data with unboosted FPV<br>APV ↓ R-methadone[e] $C_{min}$ 21%, AUC no significant change | Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar to that with APV. |
| | All PI/r | ATV/r, DRV/r, and FPV/r<br>↓ R-methadone[e] AUC 16% to 18%<br>LPV/r ↓ methadone AUC 26% to 53%<br>SQV/r 1000/100 mg BID<br>↓ R-methadone[e] AUC 19%<br>TPV/r ↓ R-methadone[e] AUC 48% | Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required, but monitor for opioid withdrawal and increase methadone dose as clinically indicated. |
| **Oxycodone** | LPV/r | oxycodone AUC ↑ 2.6-fold | Monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary. |
| **Tramadol** | ATV/c, DRV/c | ↑ tramadol possible | Tramadol dose reduction may be necessary. Monitor for tramadol toxicities and clinical response. |
| **Phosphodiesterase Type 5 (PDE5) Inhibitors** | | | |
| **Avanafil** | All PIs except unboosted ATV and FPV | RTV (600 mg BID for 5 days) ↑ avanafil AUC 13-fold, $C_{max}$ 2.4-fold | **Coadministration is not recommended.** |
| | ATV, FPV (unboosted) | No data | Avanafil dose should not exceed 50 mg once every 24 hours. |
| **Sildenafil** | All PIs | DRV/r plus sildenafil 25 mg similar to sildenafil 100 mg alone<br>RTV 500 mg BID ↑ sildenafil AUC 1,000%<br>SQV unboosted ↑ sildenafil AUC 210% | For Treatment of Erectile Dysfunction:<br>• Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.<br>For Treatment of PAH:<br>• **Contraindicated. Do not coadminister.** |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 14 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Phosphodiesterase Type 5 (PDE5) Inhibitors, continued** | | | |
| **Tadalafil** | All PIs | RTV 200 mg BID ↑ tadalafil AUC 124%<br>TPV/r (1st dose) ↑ tadalafil AUC 133%<br>TPV/r steady state: no significant effect | For Treatment of Erectile Dysfunction:<br>• Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil.<br>For Treatment of PAH<br>*In patients on a PI >7 days:*<br>• Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability.<br>*In patients on tadalafil who require a PI:*<br>• Stop tadalafil ≥24 hours before PI initiation. Seven days after PI initiation, restart tadalafil at 20 mg once daily and increase to 40 mg once daily based on tolerability.<br>*In patients switching between COBI and RTV:*<br>• Maintain tadalafil dose.<br>For Treatment of Benign Prostatic Hyperplasia:<br>Maximum recommended daily dose is 2.5 mg per day. |
| **Vardenafil** | All PIs | RTV 600 mg BID ↑ vardenafil AUC 49-fold | Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil. |
| **Sedative/Hypnotics** | | | |
| **Alprazolam, Clonazepam, Diazepam** | All PIs | ↑ benzodiazepine possible<br>RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and AUC 248% | Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam. |
| **Lorazepam, Oxazepam, Temazepam** | All PIs | No data | These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines. |
| **Midazolam** | All PIs | ↑ midazolam expected<br>SQV/r ↑ midazolam (oral) AUC 1144% and $C_{max}$ 327% | **Do not coadminister oral midazolam and PIs.**<br>Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation. |
| **Suvorexant** | All PIs | ↑ suvorexant expected | **Coadministration is not recommended.** |
| **Triazolam** | All PIs | ↑ triazolam expected<br>RTV (200 mg BID) ↑ triazolam half-life 1200% and AUC 2000% | **Do not coadminister.** |
| **Zolpidem** | PI/r or ATV/c or DRV/c | ↑ zolpidem possible | Initiate zolpidem at a low dose. Dose reduction may be necessary. |



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**Table 19a. Drug Interactions between Protease Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 15 of 15)**

| Concomitant Drug | PI | Effect on PI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Miscellaneous Drugs** | | | |
| **Colchicine** | All PIs | RTV 100 mg BID ↑ colchicine AUC 296%, $C_{max}$ 184%<br>With all PIs with or without COBI or RTV: significant ↑ colchicine expected | For Treatment of Gout Flares:<br>• Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.<br>*With FPV without RTV:*<br>• 1.2 mg x 1 dose and no repeat dose for at least 3 days<br>For Prophylaxis of Gout Flares:<br>• Colchicine 0.3 mg once daily or every other day<br>*With FPV without RTV:*<br>• Colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily<br>For Treatment of Familial Mediterranean Fever:<br>• Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.<br>*With FPV without RTV:*<br>• Do not exceed 1.2 mg once daily or 0.6 mg BID.<br>**Do not coadminister in patients with hepatic or renal impairment.** |
| **Flibanserin** | All PIs | ↑ flibanserin expected | **Contraindicated. Do not coadminister.** |
| **Salmeterol** | All PIs | ↑ salmeterol possible | **Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events. |

[a] DHA is an active metabolite of artemether.

[b] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Brevicon; Femcon Fe; Modicon; Norinyl 1/35; Ortho-Cyclen; Ortho-Novum 1/35, 7/7/7; Ortho Tri-Cyclen; Ovcon 35; Tri-Norinyl.

[c] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Lo Minastrin Fe; Lo Loestrin Fe; Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Minastrin 24 Fe; Ortho Tri-Cyclen Lo.

[d] Norbuprenorphine is an active metabolite of buprenorphine.

[e] R-methadone is the active form of methadone.

**Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change**

**Key to Acronyms:** 17-BMP = beclomethasone 17-monopropionate; APV = amprenavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DHA = dihydroartemisinin; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; ECG = electrocardiogram; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; HCV = hepatitis C virus; INR = international normalized ratio; LPV = lopinavir; LPV/r = ritonavir-boosted lopinavir; MPA = medroxyprogesterone acetate; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitorritonavir; PK = pharmacokinetic; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RAL = raltegravir; RTV = ritonavir; SQV = saquinavir; SQV/r = ritonavir-boosted saquinavir; TCA = tricyclic antidepressant; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; VPA = valproic acid

**Note:** FPV is a prodrug of APV.



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## Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 7)

This table provides information relating to PK interactions between NNRTIs and non-ARV drugs. For interactions between ARV agents and for dosing recommendations, refer to Tables 19c, 20a and 20b.

**Note:** DLV is **not** included in this table. Please refer to the DLV FDA package insert for information regarding drug interactions.

| Concomitant Drug Class/Name | NNRTI[a] | Effect on NNRTI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Acid Reducers** | | | |
| **Antacids** | RPV | ↓ RPV expected when given simultaneously | Give antacids at least 2 hours before or at least 4 hours after RPV. |
| **H2-Receptor Antagonists** | RPV | ↓ RPV | Give H2-receptor antagonists at least 12 hours before or at least 4 hours after RPV. |
| **PPIs** | RPV | With omeprazole 20 mg daily:<br>• RPV AUC ↓ 40%, $C_{min}$ ↓ 33% | **Contraindicated. Do not coadminister.** |
| **Anticoagulants/Antiplatelets** | | | |
| **Warfarin** | EFV, NVP | ↑ or ↓ warfarin possible | Monitor INR and adjust warfarin dose accordingly. |
| | ETR | ↑ warfarin possible | Monitor INR and adjust warfarin dose accordingly. |
| **Clopidogrel** | ETR | ↓ activation of clopidogrel possible | ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible. |
| **Anticonvulsants** | | | |
| **Carbamazepine<br>Phenobarbital<br>Phenytoin** | EFV | Carbamazepine plus EFV:<br>• Carbamazepine AUC ↓ 27%<br>• EFV AUC ↓ 36%<br>Phenytoin plus EFV:<br>• ↓ EFV<br>• ↓ phenytoin possible | Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed. |
| | ETR | ↓ anticonvulsant and ETR possible | **Do not coadminister.** Consider alternative anticonvulsant. |
| | NVP | ↓ anticonvulsant and NVP possible | Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant. |
| | RPV | ↓ RPV possible | **Contraindicated. Do not coadminister.** Consider alternative anticonvulsant. |
| **Oxcarbazepine** | RPV | ↓ RPV possible | **Contraindicated. Do not coadminister.** Consider alternative anticonvulsant. |
| **Antidepressants** | | | |
| **Bupropion** | EFV | Bupropion AUC ↓ 55% | Titrate bupropion dose based on clinical response. |
| **Paroxetine** | EFV, ETR | No significant effect | No dosage adjustment necessary. |
| **Sertraline** | EFV | Sertraline AUC ↓ 39% | Titrate sertraline dose based on clinical response. |



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**Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 7)**

| Concomitant Drug Class/Name | NNRTI[a] | Effect on NNRTI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antifungals** | | | |
| **Fluconazole** | EFV | No significant effect | No dosage adjustment necessary. |
| | ETR | ETR AUC ↑ 86% | No dosage adjustment necessary. Use with caution. |
| | NVP | NVP AUC ↑ 110% | Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent. |
| | RPV | ↑ RPV possible | No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. |
| **Isavuconazole** | EFV, ETR, NVP | ↓ isavuconazole possible | Dose adjustments for isavuconazole may be necessary. Consider monitoring isavuconazole level and antifungal response. |
| | RPV | ↓ isavuconazole possible (likely to a lesser extent than with other NNRTIs)<br>↑ RPV possible | No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. |
| **Itraconazole** | EFV | Itraconazole and OH-itraconazole AUC, $C_{max}$, and $C_{min}$ ↓ 35% to 44% | Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly. |
| | ETR | ↓ itraconazole possible<br>↑ ETR possible | Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response. |
| | NVP | ↓ itraconazole possible<br>↑ NVP possible | Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly. |
| | RPV | ↓ itraconazole possible<br>↑ RPV possible | No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. |
| **Posaconazole** | EFV | Posaconazole AUC ↓ 50%<br>↔ EFV | Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly. |
| | ETR | ↑ ETR possible | No dosage adjustment necessary. |
| | RPV | ↓ posaconazole possible<br>↑ RPV possible | No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. |
| **Voriconazole** | EFV | Voriconazole AUC ↓ 77%<br>EFV AUC ↑ 44% | **Contraindicated at standard doses.**<br>Dose adjustment:<br>• Voriconazole 400 mg BID, EFV 300 mg daily |
| | ETR | Voriconazole AUC ↑ 14%<br>ETR AUC ↑ 36% | No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level. |
| | NVP | ↓ voriconazole possible<br>↑ NVP possible | Monitor for toxicity and antifungal response and/or voriconazole level. |
| | RPV | ↓ voriconazole possible<br>↑ RPV possible | No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. |



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**Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 7)**

| Concomitant Drug Class/Name | NNRTI[a] | Effect on NNRTI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antimalarials** | | | |
| **Artemether/ Lumefantrine** | EFV | Artemether AUC ↓ 79%<br>DHA AUC ↓ 75%<br>Lumefantrine AUC ↓ 56% | Consider alternative ARV or antimalarial drug. If used in combination, monitor closely for antimalarial efficacy and malaria recurrence. |
| | ETR | Artemether AUC ↓ 38%<br>DHA AUC ↓ 15%<br>Lumefantrine AUC ↓ 13%<br>ETR AUC ↑ 10% | Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with ETR, monitor closely for antimalarial efficacy. |
| | NVP | Artemether AUC ↓ 67% to 72%<br>DHA:<br>• Study results are conflicting. AUC ↓ 37% in one study, no difference in another.<br>Lumefantrine:<br>• Study results are conflicting. Lumefantrine AUC ↓ 25% to 58% in 2 studies but ↑ 56% in another. | Clinical significance unknown. If used, monitor closely for antimalarial efficacy and lumefantrine toxicity. |
| **Atovaquone/ Proguanil** | EFV | Atovaquone AUC ↓ 75%<br>Proguanil AUC ↓ 43% | No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible. |
| **Antimycobacterials** | | | |
| **Bedaquiline** | EFV | ↓ bedaquiline possible | Not recommended. |
| | NVP | ↔ bedaquiline AUC | No dosage adjustment necessary. |
| **Clarithromycin** | EFV | Clarithromycin AUC ↓ 39% | Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
| | ETR | Clarithromycin AUC ↓ 39%<br>ETR AUC ↑ 42% | Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
| | NVP | Clarithromycin AUC ↓ 31% | Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
| | RPV | ↔ clarithromycin expected<br>↑ RPV possible | Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment. |
| **Rifabutin** | EFV | Rifabutin ↓ 38% | Dose:<br>• Rifabutin 450–600 mg/day; or<br>• Rifabutin 600 mg 3 times/week **if** EFV is not coadministered with a PI. |
| | ETR | Rifabutin and metabolite AUC ↓ 17%<br>ETR AUC ↓ 37% | **If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.**<br>Dose:<br>• Rifabutin 300 mg once daily **if** ETR is not coadministered with a PI/r. |
| | NVP | Rifabutin AUC ↑ 17% and metabolite AUC ↑ 24%<br>NVP $C_{min}$ ↓ 16% | No dosage adjustment necessary. Use with caution. |
| | RPV | Rifabutin plus RPV 50 mg once daily compared to RPV 25 mg once daily alone:<br>↔ RPV AUC, $C_{min}$ | Increase RPV dose to 50 mg once daily. |



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**Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 7)**

| Concomitant Drug Class/Name | NNRTI[a] | Effect on NNRTI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antimycobacterials, continued** | | | |
| **Rifampin** | EFV | EFV AUC ↓ 26% | Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring. |
| | ETR | Significant ↓ ETR possible | **Do not coadminister.** |
| | NVP | NVP ↓ 20% to 58% | **Do not coadminister.** |
| | RPV | RPV AUC ↓ 80% | **Contraindicated. Do not coadminister.** |
| **Rifapentine** | EFV | ↔ EFV concentrations | No dosage adjustment necessary. |
| | ETR, NVP, RPV | ↓ NNRTI possible | **Do not coadminister.** |
| **Antipneumocystis and Antitoxoplasmosis Drugs** | | | |
| **Atovaquone** | EFV | Atovaquone AUC ↓ 44% to 47% | Consider alternative agent for PCP or toxoplasmosis treatment or use alternative ARV drug.<br>If used in combination, monitor therapeutic efficacy of atovaquone. |
| **Benzodiazepines** | | | |
| **Alprazolam** | EFV, ETR, NVP, RPV | No data | Monitor for therapeutic effectiveness of alprazolam. |
| **Diazepam** | ETR | ↑ diazepam possible | Decreased dose of diazepam may be necessary. |
| **Lorazepam** | EFV | Lorazepam $C_{max}$ ↑ 16%, AUC ↔ | No dosage adjustment necessary. |
| **Midazolam** | EFV | Significant ↑ midazolam expected | **Do not coadminister with oral midazolam.**<br>Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation. |
| **Triazolam** | EFV | Significant ↑ triazolam expected | **Do not coadminister.** |
| **Cardiac Medications** | | | |
| **Dihydropyridine CCBs** | EFV, NVP | ↓ CCBs possible | Titrate CCB dose based on clinical response. |
| **Diltiazem<br>Verapamil** | EFV | Diltiazem AUC ↓ 69%<br>↓ verapamil possible | Titrate diltiazem or verapamil dose based on clinical response. |
| | NVP | ↓ diltiazem or verapamil possible | |
| **Corticosteroids** | | | |
| **Dexamethasone** | EFV, ETR, NVP | ↓ EFV, ETR, NVP possible | Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response. |
| | RPV | Significant ↓ RPV possible | **Contraindicated with more than a single dose of dexamethasone.** |
| **Hepatitis C Direct-Acting Antiviral Agents** | | | |
| **Daclatasvir** | EFV, ETR, NVP | Daclatasvir $C_{min}$ ↓ 17%, following daclatasvir 120 mg once daily + EFV 600 mg daily | Daclatasvir 90 mg once daily. |
| | RPV | No data | No dosage adjustment necessary. |



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**Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 7)**

| Concomitant Drug Class/Name | NNRTI[a] | Effect on NNRTI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Hepatitis C Direct-Acting Antiviral Agents, continued** | | | |
| **Dasabuvir plus Paritaprevir/ Ombitasivir/RTV** | EFV | No data | **Contraindicated. Do not coadminister.** |
| | ETR, NVP | ↓ DAAs possible | **Do not coadminister.** |
| | RPV | RPV AUC ↑ 150% to 225% | **Do not coadminister because of potential for QT interval prolongation with higher concentrations of RPV.** |
| **Elbasvir/Grazoprevir** | EFV | Elbasvir AUC ↓ 54%<br>Grazoprevir AUC ↓83%<br>EFV ↔ by grazoprevir<br>EFV ↔ AUC by elbasvir | **Contraindicated**. |
| | ETR, NVP | ↓ elbasvir, grazoprevir expected | **Do not coadminister.** |
| | RPV | Elbasvir, grazoprevir and RPV ↔ | No dosage adjustment necessary. |
| **Ledipasvir/ Sofosbuvir** | EFV | Ledipasvir AUC, $C_{min}$, $C_{max}$ – all ↓ 34%<br>Sofosbuvir: no significant effect | No dosage adjustment necessary. |
| | ETR, NVP, RPV | No significant effect expected | |
| **Simeprevir** | EFV | Simeprevir AUC ↓ 71%, $C_{min}$ ↓ 91%<br>↔ EFV | **Coadministration is not recommended.** |
| | ETR, NVP | ↓ simeprevir expected | **Coadministration is not recommended.** |
| | RPV | ↔ simeprevir and RPV | No dosage adjustment necessary. |
| **Herbal Products** | | | |
| **St. John's Wort** | EFV, ETR, NVP, RPV | ↓ NNRTI | **Do not coadminister.** |
| **Hormonal Contraceptives** | | | |
| **Hormonal Contraceptives** | EFV | Ethinyl estradiol ↔<br>Levonorgestrel (oral) AUC ↓ 64%<br>Norelgestromin AUC ↓ 64%<br>Etonogestrel (implant) AUC ↓ 63%<br>Levonorgestrel (implant) AUC ↓ 48% | Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.<br>Unintended pregnancies were observed in women who used EFV and levonorgestrel implant concomitantly. |
| | ETR | Ethinyl estradiol AUC ↑ 22%<br>Norethindrone: no significant effect | No dosage adjustment necessary. |
| | NVP | Ethinyl estradiol AUC ↓ 29%, $C_{min}$ ↓ 58%<br>Norethindrone AUC ↓ 18%<br>Etonogestrel (metabolite of oral desogestrel) ↓ 22% | Consider alternative or additional contraceptive methods. |
| | | DMPA: no significant change | No dosage adjustment necessary. |
| | | Levonorgestrel implant: AUC ↑ 30% | No dosage adjustment necessary. |
| | RPV | Ethinyl estradiol: no significant change<br>Norethindrone: no significant change | No dosage adjustment necessary. |



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**Table 19b. Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 7)**

| Concomitant Drug Class/Name | NNRTI[a] | Effect on NNRTI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Levonorgestrel**<br>For emergency contraception | EFV | Levonorgestrel AUC ↓ 58% | Effectiveness of emergency postcoital contraception may be diminished. |
| **HMG-CoA Reductase Inhibitors** | | | |
| **Atorvastatin** | EFV, ETR | Atorvastatin AUC ↓ 32% to 43% | Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose. |
| | RPV | Atorvastatin AUC ↔<br>Atorvastatin metabolites ↑ | No dosage adjustment necessary. |
| **Fluvastatin** | ETR | ↑ fluvastatin possible | Dose adjustments for fluvastatin may be necessary. |
| **Lovastatin**<br>**Simvastatin** | EFV | Simvastatin AUC ↓ 68% | Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV is used with a PI/r, simvastatin and lovastatin should be avoided. |
| | ETR, NVP | ↓ lovastatin possible<br>↓ simvastatin possible | Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP is used with a PI/r, simvastatin and lovastatin should be avoided. |
| **Pitavastatin** | EFV | Pitavastatin AUC ↓ 11%, $C_{max}$ ↑ 20% | No dosage adjustment necessary. |
| | ETR, NVP, RPV | No data | No significant effect expected. No dosage adjustment necessary. |
| **Pravastatin**<br>**Rosuvastatin** | EFV | Pravastatin AUC ↓ 44%<br>Rosuvastatin: no data | Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose. |
| | ETR | No significant effect expected | No dosage adjustment necessary. |
| **Immunosuppressants** | | | |
| **Cyclosporine**<br>**Sirolimus**<br>**Tacrolimus** | EFV, ETR, NVP | ↓ immunosuppressant possible | Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary. |
| **Narcotics/Treatments for Opioid Dependence** | | | |
| **Buprenorphine sublingual/buccal** | EFV | Buprenorphine AUC ↓ 50%<br>Norbuprenorphine[b] AUC ↓ 71% | No dosage adjustment recommended; monitor for withdrawal symptoms. |
| | ETR | Buprenorphine AUC ↓ 25% | No dosage adjustment necessary. |
| | NVP | No significant effect | No dosage adjustment necessary. |
| **Buprenorphine implant** | EFV, ETR, NVP | No data | Clinical monitoring is recommended if NNRTI is initiated after insertion of buprenorphine implant. |
| **Methadone** | EFV | Methadone AUC ↓ 52% | Opioid withdrawal common; increased methadone dose often necessary. |
| | ETR | No significant effect | No dosage adjustment necessary. |
| | NVP | Methadone AUC ↓ 37% to 51%<br>NVP: no significant effect | Opioid withdrawal common; increased methadone dose often necessary. |
| | RPV | R-methadone[c] AUC ↓ 16% | No dosage adjustment necessary, but monitor for withdrawal symptoms. |



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**Table 19b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 7)**

| Concomitant Drug Class/Name | NNRTI[a] | Effect on NNRTI and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **PDE5 Inhibitors** | | | |
| **Avanafil** | EFV, ETR, NVP, RPV | No data | **Coadministration is not recommended.** |
| **Sildenafil** | ETR | Sildenafil AUC ↓ 57% | May need to increase sildenafil dose based on clinical effect. |
| | RPV | ↔ sildenafil | No dosage adjustment necessary. |
| **Tadalafil** | ETR | ↓ tadalafil possible | May need to increase tadalafil dose based on clinical effect. |
| **Vardenafil** | ETR | ↓ vardenafil possible | May need to increase vardenafil dose based on clinical effect. |

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.

[b] Norbuprenorphine is an active metabolite of buprenorphine.

[c] R-methadone is the active form of methadone.

**Key to Symbols:** ↑ = increase, ↓ = decrease, ↔ = no change

**Key to Acronyms:** ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CCB = calcium channel blockers; $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; DAAs = direct-acting antivirals; DHA = dihydroartemisinin; DLV = delavirdine; DMPA = depot medroxyprogesterone acetate; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; HMG-CoA = hydroxy-methylglutaryl-coenzyme A; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; PCP = *Pneumocystis jiroveci* pneumonia; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RPV = rilpivirine; RTV = ritonavir



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**Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 3)**

| Concomitant Drug Class/Name | NRTI | Effect on NRTI and/or Concomitant Drug Concentrations | Dosage Recommendations and Clinical Comments |
|---|---|---|---|
| **Non-ARV Antivirals** | | | |
| **Adefovir** | TDF | No data | **Do not coadminister.** Serum concentrations of TDF and/or other renally eliminated drugs may be increased. |
| **Ganciclovir**<br>**Valganciclovir** | TDF | No data | Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities. |
| | ZDV | No significant effect | Potential increase in hematologic toxicities |
| **Ledipasvir/ Sofosbuvir** | TAF | No significant effect | No dose adjustment |
| | TDF | • Ledipasvir ↑ TDF AUC 40% to 98% when TDF given with RPV and EFV<br>• Further ↑ TDF possible if TDF given with PIs | No dose adjustment necessary. Monitor for TDF toxicity.<br>The safety of increased TDF exposure when ledipasvir/sofosbuvir is coadministered with TDF and a PI/r, ATV/c, or DRV/c has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. If coadministration is necessary, monitor for TDF-associated adverse reactions.<br>Coadministration of ledipasvir/sofosbuvir with EVG/c/TDF/FTC **is not recommended**. |
| **Ribavirin** | ddI | ↑ intracellular ddI | **Contraindicated. Do not coadminister.** Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration. |
| | ZDV | Ribavirin inhibits phosphorylation of ZDV. | Avoid coadministration if possible, or closely monitor HIV virologic response and possible hematologic toxicities. |
| **INSTIs** | | | |
| **DTG** | TAF | TAF AUC ↔ | No dosage adjustment |
| | TDF | • TDF AUC ↑ 12% and $C_{min}$ ↑ 19%<br>• DTG ↔ | No dosage adjustment |
| **RAL** | TDF | RAL AUC ↑ 49% | No dosage adjustment |
| **Narcotics/Treatment for Opioid Dependence** | | | |
| **Buprenorphine** | 3TC, ddI, TDF, TAF, ZDV | No significant effect | No dosage adjustment |
| **Methadone** | ABC | Methadone clearance ↑ 22% | No dosage adjustment |
| | d4T | d4T AUC ↓ 23% | No dosage adjustment |
| | ZDV | ZDV AUC ↑ 29% to 43% | Monitor for ZDV-related adverse effects. |
| **NNRTIs** | | | |
| **RPV** | ddI | RPV, ddI ↔ when RPV taken 2 hours after ddI | Administer RPV with food 4 hours before or 2 hours after ddI. |



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**Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 3)**

| Concomitant Drug Class/Name | NRTI | Effect on NRTI and/or Concomitant Drug Concentrations | Dosage Recommendations and Clinical Comments |
|---|---|---|---|
| **NRTIs** | | | |
| **ddI** | d4T | No significant PK interaction | **Do not coadminister.** Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination. |
| | TDF | ddI-EC AUC and $C_{max}$ ↑ 48% to 60% | **Avoid coadministration.** |
| **Other** | | | |
| **Allopurinol** | ddI | ddI AUC ↑ 113%<br>In patients with renal impairment:<br>• ddI AUC ↑ 312% | **Contraindicated.** Potential for increased ddI-associated toxicities. |
| **Atovaquone** | ZDV | ZDV AUC ↑ 31% | Monitor for ZDV-related adverse effects. |
| **Anticonvulsants** Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin | TAF | ↓ TAF possible | Consider alternative anticonvulsant. |
| **Antimycobacterial** Rifabutin, Rifampin, Rifapentine | TAF | ↓ TAF possible | Coadministration is not recommended. |
| **Herbal Products** St. John's wort | TAF | ↓ TAF possible | Coadministration is not recommended. |
| **PIs** | | | |
| **ATV +/- RTV or COBI** | ddI | With ddI-EC plus ATV (with food):<br>• ddI AUC ↓ 34%<br>• ATV no change | Administer ATV with food 2 hours before or 1 hour after ddI. |
| | TAF | TAF 10 mg with ATV/r:<br>TAF AUC ↑ 91% | No dosage adjustment (use TAF 25mg). |
| | TDF | With ATV (unboosted):<br>• ATV AUC ↓ 25% and $C_{min}$ ↓ 23% to 40% (higher $C_{min}$ with RTV than without RTV)<br>• TDF AUC ↑ 24% to 37% | **Avoid concomitant use without RTV or COBI.**<br>Dose:<br>• ATV 300 mg daily plus (RTV 100 mg or COBI 150 mg) daily when coadministered with TDF 300 mg daily.<br>• If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg daily plus (RTV 100 mg or COBI 150 mg) daily.<br>Monitor for TDF-associated toxicity. |
| | ZDV | With ATV (unboosted):<br>• ZDV $C_{min}$ ↓ 30% and AUC ↔ | Clinical significance unknown. |



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**Table 19c. Drug Interactions Between Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 3)**

| Concomitant Drug Class/Name | NRTI | Effect on NRTI and/or Concomitant Drug Concentrations | Dosage Recommendations and Clinical Comments |
|---|---|---|---|
| **DRV/c** | TAF | TAF 25 mg with DRV/c:<br>TAF AUC ↔ | No dosage adjustment |
| | TDF | Increased TDF possible | Monitor for TDF-associated toxicity. |
| **DRV/r** | TAF | TAF 10 mg with DRV/r:<br>TAF AUC ↔ | No dosage adjustment |
| | TDF | TDF AUC ↑ 22% and $C_{min}$ ↑ 37% | Clinical significance unknown. Monitor for TDF toxicity. |
| **LPV/r** | TAF | TAF 10 mg with DRV/r:<br>• TAF AUC ↑ 47% | No dosage adjustment |
| | TDF | • LPV/r AUC ↓ 15%<br>• TDF AUC ↑ 34% | Clinical significance unknown. Monitor for TDF toxicity. |
| **TPV/r** | ABC | ABC AUC ↓ 35% to 44% | Appropriate doses for this combination have not been established. |
| | ddI | ddI-EC AUC ↔ and $C_{min}$ ↓ 34%<br>TPV/r ↔ | Separate doses by at least 2 hours. |
| | TAF | ↓ TAF expected | Coadministration **is not recommended**. |
| | TDF | • TDF AUC ↔<br>• TPV/r AUC ↓ 9% to 18% and $C_{min}$ ↓ 12% to 21% | No dosage adjustment necessary. |
| | ZDV | • ZDV AUC ↓ 35%<br>• TPV/r AUC ↓ 31% to 43% | Appropriate doses for this combination have not been established. |

**Key to Symbols:** ↑ = increase, ↓ = decrease, ↔ = no change

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AUC = area under the curve; $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = douletegravir; EC = enteric coated; EFV = efavirenz; EVG/c/TDF/FTC = elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir; ZDV = zidovudine



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 11)**

This table provides information on known or predicted pharamacokinetic interactions between INSTIs (DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with either COBI or RTV. In this table, the drug interactions with EVG/c products and those with EVG plus PI/r are presented separately. When EVG is given with a PI/r, clinicians should refer to Table 19a for recommendations on the management of drug interactions of concomitant medications and the specific PI/r used with EVG.

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Acid Reducers** | | | |
| **Aluminium, Magnesium +/- Calcium-Containing Antacids**<br>Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (eg, iron, calcium supplements, multivitamins). | DTG | DTG AUC ↓ 74% if given simultaneously with antacid; DTG AUC ↓ 26% if given 2 hours before antacid | Give DTG at least 2 hours before or at least 6 hours after antacids containing polyvalent cations. |
| | EVG/c<br>EVG plus PI/r | EVG AUC ↓ 40% to 50% if given simultaneously with antacid<br>EVG AUC ↓ 15% to 20% if given 2 hours before or after antacid; ↔ with 4-hour interval | Separate EVG/c/TDF/FTC and antacid administration by more than 2 hours. |
| | RAL | Al-Mg Hydroxide Antacid:<br>• RAL $C_{min}$ ↓ 54% to 63%<br>$CaCO_3$ Antacid:<br>• RAL $C_{min}$ ↓ 32% | **Do not coadminister RAL and Al-Mg hydroxide antacids.** Use alternative acid reducing agent.<br>No dosing separation necessary when coadministering RAL and $CaCO_3$ antacids. |
| **H2-Receptor Antagonists** | EVG/c | No significant effect | No dosage adjustment necessary. |
| | EVG plus PI/r | ↔ EVG | No dosage adjustment necessary for EVG. Refer to Table 19a for information on PI/r interactions. |
| **PPIs** | DTG | No significant effect | No dosage adjustment necessary. |
| | EVG/c | No significant effect | No dosage adjustment necessary. |
| | EVG plus PI/r | ↔ EVG | No dosage adjustment necessary for EVG. Refer to Table 19a for information on PI/r interactions. |
| | RAL | RAL AUC ↑ 212% and $C_{min}$ ↑ 46% | No dosage adjustment necessary. |
| **Anticoagulants and Antiplatelets** | | | |
| **Apixaban** | EVG/c<br>EVG plus PI/r | ↑ apixaban expected | **Avoid concomitant use.** |
| **Dabigatran** | EVG/c<br>EVG plus PI/r | ↑ dabigatran possible | No dosage adjustment for dabigatran if CrCl >50 mL/min. **Avoid coadministration if CrCl <50 mL/min.** |
| **Edoxaban** | EVG/c<br>EVG plus PI/r | ↑ edoxaban expected | **Avoid concomitant use.** |
| **Rivaroxaban** | EVG/c<br>EVG plus PI/r | ↑ rivaroxaban expected | **Avoid concomitant use.** |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Anticoagulants and Antiplatelets**, continued | | | |
| **Ticagrelor** | EVG/c<br>EVG plus PI/r | ↑ ticagrelor expected | **Avoid concomitant use.** |
| **Vorapaxar** | EVG/c<br>EVG plus PI/r | ↑ vorapaxar expected | **Avoid concomitant use.** |
| **Warfarin** | EVG/c<br>EVG plus PI/r | Warfarin levels may be affected | Monitor INR and adjust warfarin dose accordingly. |
| **Anticonvulsants** | | | |
| **Carbamazepine**<br>**Phenobarbital**<br>**Phenytoin** | DTG | ↓ DTG possible | Consider alternative anticonvulsant. |
| | EVG/c | carbamazepine AUC ↑ 43%<br>EVG AUC ↓ 69% and $C_{min}$ ↓ >99%<br>↓ COBI expected | **Contraindicated. Do not coadminister.** |
| | EVG plus PI/r | ↓ EVG | Consider alternative anticonvulsant. |
| **Ethosuximide** | EVG/c<br>EVG plus PI/r | ↑ ethosuximide possible | Clinically monitor for ethosuxamide toxicities. |
| **Oxcarbazepine** | DTG<br>EVG/c<br>EVG plus PI/r | ↓ INSTI possible | Consider alternative anticonvulsant. |
| **Antidepressants/Anxiolytics/Antipsychotics**<br>Also see Sedative/Hypnotics section below. | | | |
| **Bupropion** | EVG/c | ↑ or ↓ bupropion possible | Titrate bupropion dose based on clinical response. |
| | EVG plus PI/r | ↓ bupropion possible | Titrate bupropion dose based on clinical response. |
| **Buspirone** | EVG/c<br>EVG plus PI/r | ↑ buspirone possible | Initiate buspirone at a low dose. Dose reduction may be necessary. |
| **Fluvoxamine** | EVG/c<br>EVG plus PI/r | ↑ or ↓ EVG possible | Consider alternative antidepressant or ARV. |
| **Quetiapine** | EVG/c<br>EVG plus PI/r | ↑ quetiapine AUC expected. | Initiation of quetiapine in a patient receiving EVG/c:<br>• Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse effects.<br>Initiation of EVG/c in a patient receiving a stable dose of quetiapine:<br>• Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects. |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antidepressants/Anxiolytics/Antipsychotics**, continued<br>Also see Sedative/Hypnotics section below. | | | |
| **SSRIs**<br>Citalopram<br>Escitalopram<br>Fluoxetine<br>Paroxetine<br>Sertraline | EVG/c | ↑ SSRI possible | Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response. |
| | EVG plus PI/r | ↑ or ↓ SSRI possible | Titrate SSRI dose based on clinical response. |
| | RAL | ↔ RAL<br>↔ citalopram | No dosage adjustment necessary. |
| **TCAs**<br>Amitriptyline<br>Desipramine<br>Doxepin<br>Imipramine<br>Nortriptyline | EVG/c | Desipramine AUC ↑ 65% | Initiate with lowest dose of TCA and titrate dose carefully. |
| | EVG plus PI/r | ↑ TCA expected | Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels. |
| **Trazodone** | EVG/c<br>EVG plus PI/r | ↑ trazodone possible | Initiate with lowest dose of trazodone and titrate dose carefully. |
| **Antifungals** | | | |
| **Isavuconazole** | EVG/c | ↑ isavuconazole expected<br>↑ EVG and COBI possible | If coadministered, consider monitoring isavuconazole concentrations and assess virologic response. |
| | EVG plus PI/r | Changes in isavuconazole and EVG possible | Refer to Table 19a for PI recommendations. |
| **Itraconazole** | EVG/c | ↑ itraconazole expected<br>↑ EVG and COBI possible | Consider monitoring itraconazole level to guide dosage adjustments. High itraconazole doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels. |
| | EVG plus PI/r | ↑ EVG possible | Refer to Table 19a for PI recommendations. |
| **Posaconazole** | EVG/c | ↑ EVG and COBI possible<br>↑ posaconazole possible | If coadministered, monitor posaconazole concentrations. |
| | EVG plus PI/r | ↑ EVG possible | Refer to Table 19a for PI recommendations. |
| **Voriconazole** | EVG/c | ↑ voriconazole expected<br>↑ EVG and COBI possible | Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly. |
| | EVG plus PI/r | Changes in voriconazole and EVG possible | Refer to Table 19a for PI recommendations. |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antimycobacterials** | | | |
| **Clarithromycin** | EVG/c | ↑ clarithromycin possible<br>↑ COBI possible | CrCl 50–60 mL/min:<br>• Reduce clarithromycin dose by 50%.<br>CrCl <50 mL/min:<br>• EVG/c is not recommended. |
| **Rifabutin** | DTG | Rifabutin (300 mg once daily):<br>• DTG AUC ↔ and $C_{min}$ ↓ 30% | No dosage adjustment necessary. |
| | EVG/c | Rifabutin 150 mg every other day with EVG/c once daily compared to Rifabutin 300 mg once daily alone:<br>↔ rifabutin AUC<br>25-O-desacetyl-rifabutin AUC ↑ 625%<br>EVG AUC ↓ 21%, $C_{min}$ ↓ 67% | **Do not coadminister.** |
| | EVG plus PI/r | ↔ EVG<br>↔ rifabutin AUC<br>25-O-desacetyl-rifabutin AUC ↑ 951% | Refer to Table 19a for dosing recommendations for rifabutin with PI. |
| | RAL | RAL AUC ↑ 19% and $C_{min}$ ↓ 20% | No dosage adjustment necessary. |
| **Rifampin** | DTG | Rifampin with DTG 50 mg BID compared to DTG 50 mg BID alone:<br>DTG AUC ↓ 54%, $C_{min}$ ↓ 72%<br>Rifampin with DTG 50 mg BID compared to DTG 50 mg once daily alone:<br>DTG AUC ↑ 33%, $C_{min}$ ↑ 22% | Dose:<br>DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INSTI mutation.<br>**Alternative to rifampin should be used in patients with certain suspected or documented INSTI-associated resistance substitutions. Consider using rifabutin.** |
| | EVG/c<br>EVG plus PI/r | Significant ↓ EVG and COBI expected | **Do not coadminister.** |
| | RAL | RAL 400 mg:<br>• RAL AUC ↓ 40%, $C_{min}$ ↓ 61%<br>Compared with RAL 400 mg BID alone, Rifampin with RAL 800 mg BID:<br>• RAL AUC ↑ 27%, $C_{min}$ ↓ 53% | Dose:<br>• RAL 800 mg BID<br>Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin. |
| **Rifapentine** | DTG | Significant ↓ DTG expected | **Do not coadminister.** |
| | EVG/c<br>EVG plus PI/r | Significant ↓ EVG and COBI expected | **Do not coadminister.** |
| | RAL | Rifapentine 600 mg once daily:<br>RAL $C_{min}$ ↓ 41%<br>Rifapentine 900 mg once weekly:<br>RAL AUC ↑ 71%, $C_{min}$ ↓ 12% | **Do not coadminister with once-daily rifapentine.**<br>For once-weekly rifapentine, use standard doses. |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Cardiac Medications** | | | |
| **Antiarrhythmics**<br><br>Amiodarone<br>Bepridil<br>Digoxin<br>Disopyramide<br>Dronedarone<br>Flecainide<br>Systemic lidocaine<br>Mexilitine<br>Propafenone<br>Quinidine | EVG/c | ↑ antiarrhythmics possible<br><br>digoxin $C_{max}$ ↑ 41% and AUC no significant change | Use antiarrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for antiarrhythmics. |
| | EVG plus PI/r | ↑ antiarrhythmics possible | Refer to Table 18 and 19a for use of antiarrhythmics and PI/r. |
| **Bosentan** | EVG/c | ↑ bosentan possible | In patients on EVG/c ≥10 days:<br>• Start bosentan at 62.5 mg once daily or every other day based on individual tolerability.<br><br>In patients on bosentan who require EVG/c:<br>• Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability. |
| | EVG plus PI/r | ↑ bosentan possible | Refer to Table 19a for recommendations on bosentan dosing when used with PI/r. |
| **Beta-blockers**<br>(eg, metoprolol, timolol) | EVG/c<br>EVG plus PI/r | ↑ beta-blockers possible | Beta-blocker dose may need to be decreased; adjust dose based on clinical response.<br><br>Consider using beta-blockers that are not metabolized by CYP450 enzymes (eg, atenolol, labetalol, nadolol, sotalol). |
| **CCBs** | EVG/c<br>EVG plus PI/r | ↑ CCBs possible | Coadminister with caution. Titrate CCB dose and monitor for CCB efficacy and toxicities.<br><br>Refer to Table 19a for diltiazem plus ATV/r and SQV/r recommendations. |
| **Dofetilide** | DTG | ↑ dofetilide expected | **Do not coadminister.** |
| **Eplerenone** | EVG/c<br>EVG plus PI/r | ↑ eplerenone expected | **Contraindicated. Do not coadminister.** |
| **Ivabradine** | EVG/c<br>EVG plus PI/r | ↑ ivabradine expected | **Contraindicated. Do not coadminister.** |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Corticosteroids** | | | |
| **Dexamethasone** (systemic) | EVG/c | ↓ EVG and COBI possible | Use systemic dexamethasone with caution. Monitor virologic response to ART. Consider alternative corticosteroid. |
| | EVG plus PI/r | ↓ EVG possible | |
| **Fluticasone**<br>Inhaled/Intranasal | EVG/c<br>EVG plus PI/r | ↑ fluticasone possible | Coadministration may result in adrenal insufficiency and Cushing's syndrome. Consider alternative therapy (eg, beclomethasone), particularly for long-term use. |
| **Methylprednisolone**<br>**Prednisolone**<br>**Triamcinolone**<br>Local injections, including intra-articular, epidural, intra-orbital | EVG/c<br>EVG plus PI/r | ↑ glucocorticoids expected | Coadministration may result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister.** |
| **Hepatitis C Direct Acting Antivirals** | | | |
| **Daclatasvir** | DTG | ↔ Daclatasvir | No dosage adjustment necessary. |
| | EVG/c | ↑ Daclatasvir | Decrease daclastavir dose to 30 mg once daily. |
| | EVG plus PI/r | ↑ Daclatasvir expected | Decrease daclastavir dose to 30 mg once daily, regardless of which PI/r is used, except for TPV/r. Do not coadminister EVG plus TPV/r with daclastavir. |
| | RAL | No data | No dosage adjustment necessary. |
| **Dasabuvir plus Ombitasvir/Paritaprevir/r** | DTG | No data | No dosing recommendations at this time. |
| | EVG plus PI/r<br>EVG/c | No data | **Do not coadminister.** |
| | RAL | RAL AUC ↑ 134% | No dosage adjustment necessary. |
| **Elbasvir/Grazoprevir** | DTG | ↔ Elbasvir<br>↔ Grazoprevir<br>↔ DTG | No dosage adjustment necessary. |
| | EVG plus PI/r | | Refer to Table 19a for PI dosing recommendations. |
| | EVG/c | ↑ elbasvir, grazoprevir expected | **Coadministration is not recommended.** |
| | RAL | ↔ Elbasvir<br>↔ Grazoprevir<br>RAL ↔ with elbasvir<br>RAL AUC ↑ 43% with grazoprevir | No dosage adjustment necessary. |
| **Ledipasvir/Sofosbuvir** | EVG/c | ↑ TDF and ↑ ledipasvir expected | **Do not coadminister.** |
| | EVG/c | ↔ EVG/c/TAF/FTC expected | No dosage adjustment necessary. |
| | EVG plus PI/r | ↔ EVG expected | Refer to Table 19a for PI dosing recommendations. |
| | DTG<br>RAL | ↔ DTG or RAL | No dosage adjustment necessary. |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 7 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Hepatitis C Direct Acting Antivirals**, continued | | | |
| **Simeprevir** | DTG | ↔ DTG expected | No dosage adjustment necessary. |
| | EVG/c | ↑ simeprevir expected | **Coadministration is not recommended.** |
| | EVG plus PI/r | ↔ EVG expected | **Coadministration is not recommended.** |
| | RAL | No significant effect | No dosage adjustment necessary. |
| **Sofosbuvir** | All INSTIs | No significant effect expected | No dosage adjustment necessary. |
| **Herbal Products** | | | |
| **St. John's Wort** | DTG | ↓ DTG possible | **Do not coadminister.** |
| | EVG/c<br>EVG plus PI/r | ↓ EVG and COBI possible | **Do not coadminister.** |
| **Hormonal Contraceptives** | | | |
| **Hormonal Contraceptives** | RAL | No clinically significant effect | No dosage adjustment necessary. |
| **Norgestimate/Ethinyl Estradiol** | DTG | No significant effect | No dosage adjustment necessary. |
| | EVG/c | Norgestimate AUC, $C_{max}$, and $C_{min}$ ↑ >2-fold<br>Ethinyl estradiol AUC ↓ 25% and $C_{min}$ ↓ 44% | The effects of increases in progestin (norgestimate) are not fully known and can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug, and consider alternative contraceptive method. |
| | EVG plus PI/r | ⇔ EVG | Refer to Table 19a for recommendations when used with PI/r. |
| **HMG-CoA Reductase Inhibitors** | | | |
| **Atorvastatin** | EVG/c | ↑ atorvastatin possible | Titrate statin dose slowly and use the lowest dose possible. |
| | EVG plus PI/r | ⇔ EVG expected | Refer to Table 19a for dosing recommendations when used with PI/r. |
| **Lovastatin** | EVG/c<br>EVG plus PI/r | Significant ↑ lovastatin expected | **Contraindicated. Do not coadminister.** |
| **Pitavastatin**<br>**Pravastatin** | EVG/c | No data | No dosage recommendation |
| | EVG plus PI/r | ⇔ EVG expected | Refer to Table 19a for dosing recommendations when used with PI/r. |
| **Rosuvastatin** | EVG/c | Rosuvastatin AUC ↑ 38% and $C_{max}$ ↑ 89% | Titrate statin dose slowly and use the lowest dose possible. |
| | EVG plus PI/r | ⇔ EVG expected | Refer to Table 19a for dosing recommendations when used with PI/r. |
| **Simvastatin** | EVG/c<br>EVG plus PI/r | Significant ↑ simvastatin expected | **Contraindicated. Do not coadminister.** |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 8 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Immunosuppressants** | | | |
| **Cyclosporine**<br>**Everolimus**<br>**Sirolimus**<br>**Tacrolimus** | EVG/c<br>EVG plus PI/r | ↑ immunosuppressant possible | Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary. |
| **Narcotics/Treatment for Opioid Dependence** | | | |
| **Buprenorphine Sublingual/Buccal/Implant** | EVG/c | Buprenorphine AUC ↑ 35%, $C_{max}$ ↑ 12%, and $C_{min}$ ↑ 66%<br>Norbuprenorphine AUC ↑ 42%, $C_{max}$ ↑ 24%, and $C_{min}$ ↑ 57% | No dosage adjustment necessary. Clinical monitoring is recommended. When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive. |
| | EVG plus PI/r | ↔ EVG expected | Refer to Table 19a for dosing recommendations when used with PI/r. |
| | RAL | No significant effect observed (sublingual) or expected (implant) | No dosage adjustment necessary. |
| **Methadone** | DTG | No significant effect | No dosage adjustment necessary. |
| | EVG/c | No significant effect | No dosage adjustment necessary. |
| | EVG plus PI/r | ↓ methadone | Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required. Monitor for opioid withdrawal and increase methadone dose as clinically indicated. |
| | RAL | No significant effect | No dosage adjustment necessary. |
| **Neuroleptics** | | | |
| **Perphenazine**<br>**Risperidone**<br>**Thioridazine** | EVG/c | ↑ neuroleptic possible | Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary. |
| **PDE5 Inhibitors** | | | |
| **Avanafil** | EVG/c<br>EVG plus PI/r | No data | **Coadministration is not recommended.** |
| **Sildenafil** | EVG/c<br>EVG plus PI/r | ↑ sildenafil expected | For treatment of erectile dysfunction:<br>• Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.<br>For treatment of PAH:<br>• **Contraindicated** |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 9 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **PDE5 Inhibitors**, continued | | | |
| **Tadalafil** | EVG/c<br>EVG plus PI/r | ↑ tadalafil expected | For treatment of erectile dysfunction:<br>• Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil.<br>For treatment of PAH<br>*In patients on EVG/c >7 days:*<br>• Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability.<br>*In patients on tadalafil who require EVG/c:*<br>• Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily, and increase to 40 mg once daily based on tolerability. |
| **Vardenafil** | EVG/c<br>EVG plus PI/r | ↑ vardenafil expected | Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil. |
| **Sedative/Hypnotics** | | | |
| **Clonazepam**<br>**Clorazepate**<br>**Diazepam**<br>**Estazolam**<br>**Flurazepam** | EVG/c<br>EVG plus PI/r | ↑ benzodiazepines possible | Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor.<br>Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam. |
| **Midazolam**<br>**Triazolam** | DTG | With DTG 25 mg:<br>midazolam AUC ↔ | No dosage adjustment necessary. |
| | EVG/c<br>EVG plus PI/r | ↑ midazolam expected<br>↑ triazolam expected | **Do not coadminister triazolam or oral midazolam and EVG/c or (EVG plus PI).**<br>Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if more than one dose is administered. |
| **Suvorexant** | EVG/c<br>EVG plus PI/r | ↑ suvorexant expected | **Coadministration is not recommended.** |
| **Zolpidem** | EVG/c<br>EVG plus PI/r | ↑ zolpidem expected | Initiate zolpidem at a low dose. Dose reduction may be necessary. |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 10 of 11)**

| Concomitant Drug Class/Name | INSTI | Effect on INSTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Miscellaneous Drugs** | | | |
| **Colchicine** | EVG/c<br>EVG plus PI/r | ↑ colchicine expected | **Do not coadminister in patients with hepatic or renal impairment.**<br>For treatment of gout flares:<br>• Colchicine 0.6 mg for 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.<br>For prophylaxis of gout flares:<br>• If original dose was colchicine 0.6 mg BID, decrease to colchicine 0.3 mg once daily. If regimen was 0.6 mg once daily, decrease to 0.3 mg every other day.<br>For treatment of familial Mediterranean fever:<br>• Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. |
| **Flibanserin** | EVG/c<br>EVG plus PI/r | ↑ flibanserin expected | **Contraindicated. Do not coadminister.** |
| **Metformin** | DTG | DTG 50 mg once daily plus metformin 500 mg BID:<br>Metformin AUC ↑ 79%, $C_{max}$ ↑ 66%<br>DTG 50 mg BID plus metformin 500 mg BID:<br>Metformin AUC ↑ 2.4 fold, $C_{max}$ ↑ 2 fold | Limit metformin dose to no more than 1,000 mg per day.<br>When starting/stopping DTG in patient on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize GI symptoms. |
| **Polyvalent Cation Supplements**<br>Mg, Al, Fe, Ca, Zn, including multivitamins with minerals<br>**Note:** Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids. | All INSTIs | ↓ INSTI possible<br>DTG ↔ when administered with Ca or Fe supplement simultaneously with food | If coadministration is necessary, give INSTI at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic efficacy.<br>DTG and supplements containing Ca or Fe can be taken simultaneously with food.<br>Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown. |
| **Salmeterol** | EVG/c<br>EVG plus PI/r | ↑ salmeterol possible | **Do not coadminister** due to potential increased risk of salmeterol-associated cardiovascular events. |



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**Table 19d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated July 14, 2016; last reviewed July 14, 2016) (page 11 of 11)**

**Key to Acronyms:** Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; Ca = calcium; CaCO3 = calcium carbonate; CCB = calcium channel blocker; $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; c or COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; GI = gastrointestinal; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PPI = proton pump inhibitor; RAL = raltegravir; SQV/r = saquanavir/ritonavir; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; Zn = zinc



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**Table 19e. Drug Interactions between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 3)**

| Concomitant Drug Class/Name | CCR5 Antagonist | Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Anticonvulsants** | | | |
| **Carbamazepine, Phenobarbital, Phenytoin** | MVC | ↓ MVC possible | If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent. |
| **Antifungals** | | | |
| **Isavuconazole** | MVC | ↑ MVC possible | Consider dose reduction to MVC 150 mg BID. |
| **Itraconazole** | MVC | ↑ MVC possible | Dose:<br>• MVC 150 mg BID |
| **Posaconazole** | MVC | ↑ MVC possible | Dose:<br>• MVC 150 mg BID |
| **Voriconazole** | MVC | ↑ MVC possible | Consider dose reduction to MVC 150 mg BID. |
| **Antimycobacterials** | | | |
| **Clarithromycin** | MVC | ↑ MVC possible | Dose:<br>• MVC 150 mg BID |
| **Rifabutin** | MVC | ↓ MVC possible | If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID.<br>If used with a strong CYP3A inhibitor, use MVC 150 mg BID. |
| **Rifampin** | MVC | MVC AUC ↓ 64% | **Coadministration is not recommended.**<br>If coadministration is necessary, use MVC 600 mg BID.<br>If coadministered with a strong CYP3A inhibitor, use MVC 300 mg BID. |
| **Rifapentine** | MVC | ↓ MVC expected | **Do not coadminister.** |
| **Hepatitis C Direct Acting Antivirals** | | | |
| **Daclatasvir** | MVC | ↔ MVC expected<br>↔ Daclatasvir expected | **No dose adjustment for daclatasvir. MVC dose 300 mg BID.** |
| **Dasabuvir + Ombitasvir/ Paritaprevir/RTV** | MVC | ↑ MVC expected | **Do not coadminister.** |
| **Elbasvir/ Grazoprevir** | MVC | No data | No dosing recommendations at this time |
| **Ledipasvir/ Sofosbuvir** | MVC | ↔ MVC expected<br>↔ Daclatasvir expected | Dose:<br>• MVC 300 mg BID |
| **Simeprevir** | MVC | ↔ MVC expected | Dose:<br>• MVC 300 mg BID |
| **Sofosbuvir** | MVC | ↔ MVC expected | Dose:<br>• MVC 300 mg BID |



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**Table 19e. Drug Interactions Between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 3)**

| Concomitant Drug Class/Name | CCR5 Antagonist | Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Herbal Products** | | | |
| **St. John's Wort** | MVC | ↓ MVC possible | **Coadministration is not recommended.** |
| **Hormonal Contraceptives** | | | |
| **Hormonal Contraceptives** | MVC | No significant effect on ethinyl estradiol or levonorgestrel | Safe to use in combination |
| **ARV Drugs** | | | |
| **INSTIs** | | | |
| **EVG/c** | MVC | ↑ MVC possible | **Do not coadminister.** |
| **EVG + PI/r** | MVC | No data | Refer to PIs listed below for dosing recommendations when MVC is used with a PI/r. |
| **RAL** | MVC | MVC AUC ↓ 21%<br>RAL AUC ↓ 37% | Dose:<br>• Standard |
| **NNRTIs** | | | |
| **EFV** | MVC | MVC AUC ↓ 45% | Dose:<br>• MVC 600 mg BID |
| **ETR** | MVC | MVC AUC ↓ 53% | Dose:<br>• MVC 600 mg BID in the absence of a potent CYP3A inhibitor |
| **NVP** | MVC | MVC AUC ↔ | Without HIV PI:<br>• MVC 300 mg BID<br>With HIV PI (except TPV/r):<br>• MVC 150 mg BID |
| **PIs** | | | |
| **ATV +/- RTV or COBI** | MVC | With Unboosted ATV:<br>• MVC AUC ↑ 257%<br>With (ATV 300 mg Plus RTV 100 mg) Once Daily:<br>• MVC AUC ↑ 388% | Dose:<br>• MVC 150 mg BID |
| **DRV/r or DRV/c** | MVC | With (DRV 600 mg Plus RTV 100 mg) BID:<br>• MVC AUC ↑ 305%<br>With (DRV 600 mg Plus RTV 100 mg) BID and ETR:<br>• MVC AUC ↑ 210% | Dose:<br>• MVC 150 mg BID |
| **FPV +/- RTV** | MVC | With (FPV 700 mg Plus RTV 100 mg) BID and MVC 300 mg BID:<br>• MVC AUC ↑ 149%, $C_{min}$ ↑ 374%<br>With (FPV 1400 mg Plus RTV 200 mg) Once Daily and MVC 300 mg Once Daily:<br>• MVC AUC ↑ 126%, $C_{min}$ ↑ 80% | Dose:<br>• MVC 150 mg BID |
| **LPV/r** | MVC | MVC AUC ↑ 295%<br>With LPV/r and EFV:<br>• MVC AUC ↑ 153% | Dose:<br>• MVC 150 mg BID |



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**Table 19e. Drug Interactions Between CCR5 Antagonist (Maraviroc) and Other Drugs (Including Antiretroviral Agents) (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 3)**

| Concomitant Drug Class/Name | CCR5 Antagonist | Effect on CCR5 Antagonist and/or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **PIs, continued** | | | |
| **RTV** | MVC | With RTV 100 mg BID:<br>• MVC AUC ↑ 161% | Dose:<br>• MVC 150 mg BID |
| **SQV/r** | MVC | With (SQV 1000 mg Plus RTV 100 mg) BID:<br>• MVC AUC ↑ 877%<br><br>With (SQV 1000 mg Plus RTV 100 mg) BID and EFV:<br>• MVC AUC ↑ 400% | Dose:<br>• MVC 150 mg BID |
| **TPV/r** | MVC | With (TPV 500 mg Plus RTV 200 mg) BID:<br>• MVC AUC ↔ | Dose:<br>• MVC 300 mg BID |

**Note:** FPV is a prodrug of APV.

**Key to Symbols:** ↑ = increase, ↓ = decrease, ↔ = no change

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir



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**Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors[a] (Last updated September 9, 2016; last reviewed April 8, 2015) (Page 1 of 3)**

**Note:** DLV, IDV, and NFV are **not** included in this table. Refer to the DLV, IDV, and NFV Food and Drug Administration package inserts for information regarding drug interactions.

| PIs | | NNRTIs | | | |
|---|---|---|---|---|---|
| | | **EFV** | **ETR** | **NVP** | **RPV[a]** |
| **ATV** Unboosted | **PK Data** | EFV: no significant change<br>ATV AUC ↓ 74% | ETR AUC ↑ 50% and $C_{min}$ ↑ 58%<br>ATV AUC ↓ 17% and $C_{min}$ ↓ 47% | ↓ ATV possible | ↑ RPV possible |
| | **Dose** | **Do not coadminister.** | **Do not coadminister.** | **Do not coadminister.** | Standard doses |
| **ATV/c** | **PK Data** | ↓ ATV<br>↓ COBI | ↓ ATV<br>↓ COBI | ↓ COBI | ↑ RPV possible<br>↔ ATV expected |
| | **Dose** | EFV standard dose<br>In ART-Naive Patients:<br>• ATV 400 mg plus COBI 150 mg Once Daily<br>**Do not coadminister in ART-experienced patients.** | **Do not coadminister.** | **Do not coadminister.** | Standard doses |
| **ATV/r** | **PK Data** | (ATV 300 mg plus RTV 100 mg) Once Daily:<br>• ATV concentrations are similar to those with unboosted ATV without EFV. | (ATV 300 mg plus RTV 100 mg) Once Daily:<br>• ETR AUC and $C_{min}$ both ↑ ~30%<br>• ATV AUC ↔ and $C_{min}$ ↓ 18% | (ATV 300 mg plus RTV 100 mg) Once Daily:<br>• ATV AUC ↓ 42% and $C_{min}$ ↓ 72%<br>• NVP AUC ↑ 25% | ↑ RPV possible |
| | **Dose** | EFV standard dose<br>In ART-Naive Patients:<br>• (ATV 400 mg plus RTV 100 mg) Once Daily<br>**Do not coadminister in ART-experienced patients.** | ETR standard dose<br>(ATV 300 mg plus RTV 100 mg) Once Daily | **Do not coadminister.** | Standard doses |
| **DRV/c** | **PK Data** | ↓ DRV possible<br>↓ COBI possible | Effect on DRV unknown<br>↓ COBI possible | Effect on DRV unknown<br>↓ COBI possible | ↔ DRV expected<br>↑ RPV possible |
| | **Dose** | **Do not coadminister.** | **Do not coadminister.** | **Do not coadminister.** | Standard doses |



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**Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated September 9, 2016; last reviewed April 8, 2015) (Page 2 of 3)**

| PIs | | NNRTIs | | | |
|---|---|---|---|---|---|
| | | EFV | ETR | NVP | RPV[a] |
| DRV/r | PK Data | With (DRV 300 mg plus RTV 100 mg) BID:<br>• EFV AUC ↑ 21%<br>• DRV AUC ↓ 13% and $C_{min}$ ↓ 31% | ETR 100 mg BID with (DRV 600 mg plus RTV 100 mg) BID:<br>• ETR AUC ↓ 37% and $C_{min}$ ↓ 49%<br>• DRV: no significant change | With (DRV 400 mg plus RTV 100 mg) BID:<br>• NVP AUC ↑ 27% and $C_{min}$ ↑ 47%<br>• DRV AUC ↑ 24%[b] | RPV 150 mg Once Daily with (DRV 800 mg plus RTV 100 mg) Once Daily:<br>• RPV AUC ↑ 130% and $C_{min}$ ↑ 178%<br>• DRV: no significant change |
| | Dose | Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels. | Standard doses<br>Safety and efficacy of this combination, despite reduced ETR concentration, have been established in a clinical trial. | Standard doses | Standard doses |
| FPV +/- RTV | PK Data | With (FPV 1400 mg plus RTV 200 mg) Once Daily:<br>• APV $C_{min}$ ↓ 36% | With (FPV 700 mg plus RTV 100 mg) BID:<br>• APV AUC ↑ 69% and $C_{min}$ ↑ 77% | With Unboosted FPV 1400 mg BID:<br>• NVP AUC ↑ 29%<br>• APV AUC ↓ 33%<br>With (FPV 700 mg plus RTV 100 mg) BID:<br>• NVP $C_{min}$ ↑ 22% | With Boosted and Unboosted FPV:<br>• ↑ RPV possible |
| | Dose | (FPV 1400 mg plus RTV 300 mg) Once Daily **or** (FPV 700 mg plus RTV 100 mg) BID<br>EFV standard dose | **Do not coadminister with FPV +/− RTV.** | (FPV 700 mg plus RTV 100 mg) BID<br>NVP standard dose | Standard doses |
| LPV/r | PK Data | With LPV/r Tablets 500/125 mg[c] BID:<br>• LPV concentration similar to that with LPV/r 400/100 mg BID without EFV | With LPV/r Tablets:<br>• ETR AUC ↓ 35% (comparable to the decrease with DRV/r)<br>• LPV AUC ↓ 13% | With LPV/r Capsules:<br>• LPV AUC ↓ 27% and $C_{min}$ ↓ 51% | RPV 150 mg Once Daily with LPV/r Capsules:<br>• RPV AUC ↑ 52% and $C_{min}$ ↑ 74%<br>• LPV no significant change |
| | Dose | LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 520/130 mg BID<br>EFV standard dose | Standard doses | LPV/r tablets 500/125 mgc BID; LPV/r oral solution 533/133 mg BID<br>NVP standard dose | Standard doses |



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**Table 20a. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, and Protease Inhibitors[a] (Last updated September 9, 2016; last reviewed April 8, 2015) (Page 3 of 3)**

| PIs | | NNRTIs | | | |
|---|---|---|---|---|---|
| | | EFV | ETR | NVP | RPV[a] |
| **SQV** Always use with RTV | **PK Data** | With SQV 1200 mg TID:<br>• EFV AUC ↓ 12%<br>• SQV AUC ↓ 62% | With (SQV 1000 mg plus RTV 100 mg) BID:<br>• ETR AUC ↓ 33% and $C_{min}$ ↓ 29%<br>• SQV AUC ↔<br>↓ ETR levels similar to reduction with DRV/r | With SQV 600 mg TID:<br>• NVP: no significant change<br>• SQV AUC ↓ 24% | ↑ RPV possible |
| | **Dose** | (SQV 1000 mg plus RTV 100 mg) BID | (SQV 1000 mg plus RTV 100 mg) BID | Dose with SQV/r not established | Standard doses |
| **TPV** Always use with RTV | **PK Data** | With (TPV 500 mg plus RTV 100 mg) BID:<br>• EFV no significant change<br>• TPV AUC ↓ 31% and $C_{min}$ ↓ 42%<br>With (TPV 750 mg plus RTV 200 mg) BID:<br>• EFV: no significant change<br>• TPV: no significant change | With (TPV 500 mg plus RTV 200 mg) BID:<br>• ETR AUC ↓ 76% and $C_{min}$ ↓ 82%<br>• TPV AUC ↑ 18% and $C_{min}$ ↑ 24% | With (TPV 250 mg plus RTV 200 mg) BID or with (TPV 750 mg plus RTV 100 mg) BID:<br>• NVP: no significant change<br>• TPV: no data | ↑ RPV possible |
| | **Dose** | Standard doses | **Do not coadminister.** | Standard doses | Standard doses |

[a] Approved dose for RPV is 25 mg once daily. Most PK studies were performed using 75 mg to 150 mg RPV per dose.

[b] Based on between-study comparison.

[c] Use a combination of two LPV/r 200 mg/50 mg tablets plus one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.

**Key to Symbols:** ↑ = increase, ↓ = decrease, ↔ = no change

**Key to Acronyms:** APV = amprenavir; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AUC = area under the curve; BID = twice daily; $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; CYP = cytochrome P; DLV = delavirdine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FPV = fosamprenavir; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NVP = nevirapine; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TID = three times a day; TPV = tipranavir



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**Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 4)**

| ARV Drugs by Drug Class | | INSTIs | | | |
|---|---|---|---|---|---|
| | | DTG | EVG/c | EVG (when used with PI/r) | RAL |
| **NNRTIs** | | | | | |
| **EFV** | **PK Data** | With DTG 50 mg once daily:<br>• DTG AUC ↓ 57% and $C_{min}$ ↓ 75% | ↑ or ↓ EVG, COBI, EFV possible | ↓ EVG expected | RAL:<br>• AUC ↓ 36% |
| | **Dose** | In patients without INSTI resistance:<br>• DTG 50 mg BID<br>In patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance:<br>• **Consider alternative combination.** | **Do not coadminister.** | **Do not coadminister.** | Standard doses |
| **ETR** | **PK Data** | ETR 200 mg BID plus DTG 50 mg once daily:<br>• DTG AUC ↓ 71% and $C_{min}$ ↓ 88%<br>ETR 200 mg BID with (DRV 600 mg plus RTV 100 mg) BID and DTG 50 mg once daily:<br>• DTG AUC ↓ 25% and $C_{min}$ ↓ 37%<br>ETR 200 mg BID with (LPV 400 mg plus RTV 100 mg) BID and DTG 50 mg once daily:<br>• DTG AUC ↑ 11% and $C_{min}$ ↑ 28% | ↑ or ↓ EVG, COBI, ETR possible | No significant interaction between EVG/r and ETR | • ETR $C_{min}$ ↓ 17%<br>• RAL $C_{min}$ ↓ 34% |
| | **Dose** | **Do not coadminister ETR and DTG without concurrently administering ATV/r, DRV/r, or LPV/r.**<br>In patients without INSTI resistance:<br>• DTG 50 mg once daily with ETR (concurrently with ATV/r, DRV/r, or LPV/r)<br>In patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance:<br>• DTG 50 mg BID with ETR (concurrently with ATV/r, DRV/r, or LPV/r) | **Do not coadminister.** | May coadminister EVG with ETR plus (ATV/r, DRV/r, or LPV/r)<br>EVG:<br>• Standard dose depending on the concomitant PI (see below) | Standard doses |



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**Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 4)**

| ARV Drugs by Drug Class | | INSTIs | | | |
|---|---|---|---|---|---|
| | | DTG | EVG/c | EVG (when used with PI/r) | RAL |
| **NNRTIs**, continued | | | | | |
| **NVP** | **PK Data** | With DTG 50 mg once daily:<br>DTG AUC ↓ 19% and $C_{min}$ ↓ 34% | ↑ or ↓ EVG, COBI, NVP possible | ↓ EVG possible | No data |
| | **Dose** | Standard doses | **Do not coadminister.** | **Do not coadminister.** | Standard doses |
| **RPV** | **PK Data** | With DTG 50 mg once daily:<br>• DTG AUC ↔ and $C_{min}$ ↑ 22%<br>• RPV AUC ↔ and $C_{min}$ ↑ 21% | ↑ or ↓ EVG, COBI, RPV possible | ↑ RPV expected | • RPV ↔<br>• RAL $C_{min}$ ↑ 27% |
| | **Dose** | Standard doses | **Do not coadminister.** | EVG:<br>• Standard dose depending on the concomitant PI (see below)<br>RPV:<br>• Standard dose | Standard doses |
| **PIs** | | | | | |
| **ATV/c** | **PK Data** | No data | ATV/c plus EVG/c:<br>• No data | No data | No data |
| | **Dose** | Standard doses | **Do not coadminister.** | **Do not coadminister.** | Standard doses |
| **ATV +/- RTV** | **PK Data** | Unboosted ATV plus DTG 30 mg once daily:<br>• DTG AUC ↑ 91% and $C_{min}$ ↑ 180%<br>(ATV 300 mg plus RTV 100 mg) once daily plus DTG 30 mg once daily:<br>• DTG AUC ↑ 62% and $C_{min}$ ↑ 121% | ↑ or ↓ EVG, COBI, ATV possible | EVG 85 mg with (ATV 300 mg plus RTV 100 mg) once daily:<br>• EVG AUC ↔ and $C_{min}$ ↑ 38%<br>• ATV AUC and $C_{min}$ ↔ | With unboosted ATV:<br>• RAL AUC ↑ 72%<br>With (ATV 300 mg plus RTV 100 mg) once daily:<br>• RAL AUC ↑ 41% |
| | **Dose** | Standard doses | **Do not coadminister.** | • EVG 85 mg once daily<br>• (ATV 300 mg plus RTV 100 mg) once daily | Standard doses |
| **DRV/c** | **PK Data** | No data | DRV/c plus EVG/c:<br>• ↓ EVG possible | No data | No data |
| | **Dose** | Standard doses | **Do not coadminister.** | **Do not coadminister.** | Standard doses |



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**Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 4)**

| ARV Drugs by Drug Class | | INSTIs | | | |
|---|---|---|---|---|---|
| | | DTG | EVG/c | EVG (when used with PI/r) | RAL |
| **PIs**, continued | | | | | |
| **DRV/r** | **PK Data** | (DRV 600 mg plus RTV 100 mg) BID with DTG 30 mg once daily:<br>• DTG AUC ↓ 22% and $C_{min}$ ↓ 38% | ↑ or ↓ EVG, COBI, DRV possible | EVG 125 mg once daily with (DRV 600 mg plus RTV 100 mg) BID:<br>• EVG AUC and $C_{min}$ ↔<br>• DRV AUC and $C_{min}$ ↔ | With (DRV 600 mg plus RTV 100 mg) BID:<br>• RAL AUC ↓ 29% and $C_{min}$ ↑ 38% |
| | **Dose** | Standard doses:<br>• Once or twice daily dosing of DRV/r | **Do not coadminister.** | • EVG 150 mg once daily<br>• (DRV 600 mg plus RTV 100 mg) BID | Standard doses |
| **FPV +/- RTV** | **PK Data** | With (FPV 700 mg plus RTV 100 mg) BID and DTG 50 mg once daily:<br>• DTG AUC ↓ 35% and $C_{min}$ ↓ 49% | ↑ or ↓ EVG, COBI, FPV possible | No significant interaction with FPV and EVG | FPV: No significant effect |
| | **Dose** | In patients without INSTI resistance:<br>• DTG 50 mg BID<br>In patients with certain INSTI-associated resistance[a] or clinically suspected INSTI resistance:<br>• **Consider alternative combination.** | **Do not coadminister.** | • EVG 150 mg once daily<br>• (FPV 700 mg plus RTV 100 mg) BID | Standard doses |
| **LPV/r** | **PK Data** | With (LPV 400 mg plus RTV 100 mg) BID and DTG 30 mg once daily:<br>• DTG: no significant effect | ↑ or ↓ EVG, COBI, LPV possible<br>RTV and COBI have similar effects on CYP3A. | EVG 125 mg once daily with (LPV 400 mg plus RTV 100 mg) BID:<br>• EVG AUC ↑ 75% and $C_{min}$ ↑ 138%<br>• LPV AUC and $C_{min}$ ↔ | • ↓ RAL<br>• ↔ LPV/r |
| | **Dose** | Standard doses:<br>• Once or twice daily dosing of LPV/r | **Do not coadminister.** | • EVG 85 mg once daily<br>• (LPV 400 mg plus RTV 100 mg) BID | Standard doses |
| **SQV/r** | **PK Data** | No data | ↑ or ↓ EVG, COBI, SQV possible<br>RTV and COBI have similar effects on CYP3A. | No data | No data |
| | **Dose** | Standard doses | **Do not coadminister.** | No dosage recommendation | Standard doses |



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**Table 20b. Interactions between Integrase Strand Transfer Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 4)**

| ARV Drugs by Drug Class | | INSTIs | | | |
|---|---|---|---|---|---|
| | | DTG | EVG/c | EVG (when used with PI/r) | RAL |
| **PIs**, continued | | | | | |
| TPV/r | **PK Data** | With (TPV 500 mg plus RTV 200 mg) BID and DTG 50 mg once daily:<br>• DTG AUC ↓ 59% and $C_{min}$ ↓ 76% | ↑ or ↓ EVG, COBI, TPV possible<br>RTV and COBI have similar effects on CYP3A. | EVG 200 mg once daily with (TPV 500 mg plus RTV 200 mg) BID:<br>• EVG AUC and $C_{min}$ ↔<br>• TPV AUC and $C_{min}$ ↔ | With (TPV 500 mg plus RTV 200 mg) BID:<br>• RAL AUC ↓ 24% |
| | **Dose** | In patients without INSTI resistance:<br>• DTG 50 mg BID<br>In patients with certain INSTI-associated resistancea or clinically suspected INSTI resistance:<br>• **Consider alternative combination.** | **Do not coadminister.** | • EVG 150 mg once daily<br>• (TPV 500 mg plus RTV 200 mg) BID | Standard doses |

[a] Refer to dolutegravir product labeling for details.

**Key to Symbols:** ↑ = increase; ↓ = decrease; ↔ = no change

**Key to Abbreviations:** ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; BID = twice daily; $C_{min}$ = minimum plasma concentration; COBI, c = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; EVG/c/TDF/FTC = elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine; EVG/r = elvitegravir/ritonavir; FPV = fosamprenavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TPV = tipranavir; TPV/r = tipranavir/ritonavir



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**Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 6)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination | Serum/ Intracellular Half-Lives | Adverse Events[b] |
|---|---|---|---|---|---|
| **Abacavir** (ABC) *Ziagen*<br>**Note:** Generic available in tablet formulation<br>**Also available as a component of fixed-dose combinations (by trade name and abbreviation):** | Ziagen:<br>• 300 mg tablet<br>• 20 mg/mL oral solution | Ziagen:<br>• 300 mg BID, *or*<br>• 600 mg once daily<br>• Take without regard to meals | Metabolized by alcohol dehydrogenase and glucuronyl transferase<br>Renal excretion of metabolites: 82%<br>Dosage adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix B, Table 7). | 1.5 hours/ 12–26 hours | • HSRs: Patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC.<br>• For patients with history of HSR, re-challenge is not recommended.<br>• Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath.<br>• Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies. |
| *Trizivir* (ABC/ZDV/3TC)<br>**Note:** Generic available | Trizivir:<br>• (ABC 300 mg plus ZDV 300 mg plus 3TC 150 mg) tablet | Trizivir:<br>• 1 tablet BID | | | |
| *Epzicom* (ABC/3TC) | Epzicom:<br>• (ABC 600 mg plus 3TC 300 mg) tablet | Epzicom:<br>• 1 tablet once daily | | | |
| *Triumeq* (ABC/3TC/DTG) | Triumeq:<br>• (ABC 600 mg plus 3TC 300 mg plus DTG 50 mg) tablet | Triumeq:<br>• 1 tablet once daily | | | |
| **Didanosine** (ddI) *Videx*<br>*Videx EC*<br>**Note:** Generic available; dose same as Videx or Videx EC | Videx EC:<br>• 125, 200, 250, and 400 mg capsules<br>Videx:<br>• 10 mg/mL oral solution | Body Weight ≥60 kg:<br>• 400 mg once daily<br>*With TDF:*<br>• 250 mg once daily<br>Body Weight <60 kg:<br>• 250 mg once daily<br>*With TDF:*<br>• 200 mg once daily<br>Take 1/2 hour before or 2 hours after a meal.<br>**Note:** Preferred dosing with oral solution is BID (total daily dose divided into 2 doses). | Renal excretion: 50%<br>Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7). | 1.5 hours/ >20 hours | • Pancreatitis<br>• Peripheral neuropathy<br>• Retinal changes, optic neuritis<br>• Lactic acidosis with hepatic steatosis with or without pancreatitis (rare but potentially life-threatening toxicity)<br>• Nausea, vomiting<br>• Potential association with non-cirrhotic portal hypertension; in some cases, patients presented with esophageal varices<br>• One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies.<br>• Insulin resistance/diabetes mellitus |



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**Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 6)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination | Serum/ Intracellular Half-Lives | Adverse Events[b] |
|---|---|---|---|---|---|
| **Emtricitabine** (FTC) *Emtriva*<br>**Also available as a component of fixed-dose combinations (by trade name and abbreviation):** | Emtriva:<br>• 200 mg hard gelatin capsule<br>• 10 mg/mL oral solution | Emtriva:<br>*Capsule:*<br>• 200 mg once daily<br>*Oral Solution:*<br>• 240 mg (24 mL) once daily<br>Take without regard to meals. | Renal excretion: 86%<br>Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7). | 10 hours/ >20 hours | • Minimal toxicity<br>• Hyperpigmentation/skin discoloration<br>• Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC. |
| *Atripla* (FTC/EFV/TDF) | Atripla:<br>• (FTC 200 mg plus EFV 600 mg plus TDF 300 mg) tablet | Atripla:<br>• 1 tablet at or before bedtime<br>• Take on an empty stomach to reduce side effects. | | | |
| *Complera* (FTC/RPV/TDF) | Complera:<br>• (FTC 200 mg plus RPV 25 mg plus TDF 300 mg) tablet | Complera:<br>• 1 tablet once daily with a meal | | | |
| *Descovy* (FTC/TAF) | Descovy:<br>• (FTC 200 mg plus TAF 25 mg) tablet | Descovy:<br>• 1 tablet once daily | | | |
| *Genvoya* (FTC/EVG/c/TAF) | Genvoya:<br>• (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TAF 10 mg) tablet | Genvoya:<br>• 1 tablet once daily with food | | | |
| *Odefsey* (FTC/RPV/TAF) | Odefsey:<br>• (FTC 200 mg plus RPV 25 mg plus TAF 25 mg) tablet | Odefsey:<br>• 1 tablet once daily with a meal | | | |
| *Stribild* (FTC/EVG/c/TDF) | Stribild:<br>• (FTC 200 mg plus EVG 150 mg plus COBI 150 mg plus TDF 300 mg) tablet | Stribild:<br>• 1 tablet once daily with food | | | |
| *Truvada* (FTC/TDF) | Truvada:<br>• (FTC 200 mg plus TDF 300 mg) tablet | Truvada:<br>• 1 tablet once daily | | | |



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**Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 6)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination | Serum/ Intracellular Half-Lives | Adverse Events[b] |
|---|---|---|---|---|---|
| **Lamivudine** (3TC) *Epivir*<br>**Note:** Generic available<br>**Also available as a component of fixed-dose combinations (by trade name and abbreviation):** | Epivir:<br>• 150 and 300 mg tablets<br>• 10 mg/mL oral solution | Epivir:<br>• 150 mg BID, *or*<br>• 300 mg once daily<br>• Take without regard to meals. | Renal excretion: 70%<br>Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7). | 5–7 hours/ 18–22 hours | • Minimal toxicity<br>• Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC. |
| *Combivir* (3TC/ZDV)<br>**Note:** Generic available | Combivir:<br>• (3TC 150 mg plus ZDV 300 mg) tablet | Combivir:<br>• 1 tablet BID | | | |
| *Epzicom* (3TC/ABC) | Epzicom:<br>• (3TC 300 mg plus ABC 600 mg) tablet | Epzicom:<br>• 1 tablet once daily | | | |
| *Trizivir* (3TC/ZDV/ABC)<br>**Note:** Generic available | Trizivir:<br>• (3TC 150 mg plus ZDV 300 mg plus ABC 300 mg) tablet | Trizivir:<br>• 1 tablet BID | | | |
| *Triumeq* (3TC/ABC/DTG) | Triumeq:<br>• (3TC 300 mg plus ABC 600 mg plus DTG 50 mg) tablet | Triumeq:<br>• 1 tablet once daily | | | |
| **Stavudine** (d4T) *Zerit*<br>**Note:** Generic available | Zerit:<br>• 15, 20, 30, and 40 mg capsules<br>• 1 mg/mL oral solution | Body Weight ≥60 kg:<br>• 40 mg BID<br>Body Weight <60 kg:<br>• 30 mg BID<br>Take without regard to meals.<br>**Note:** WHO recommends 30 mg BID dosing regardless of body weight. | Renal excretion: 50%<br>Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7). | 1 hour/7.5 hours | • Peripheral neuropathy<br>• Lipoatrophy<br>• Pancreatitis<br>• Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity)<br>• Hyperlipidemia<br>• Insulin resistance/diabetes mellitus<br>• Rapidly progressive ascending neuromuscular weakness (rare) |



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**Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 6)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination | Serum/ Intracellular Half-Lives | Adverse Events[b] |
|---|---|---|---|---|---|
| **Tenofovir Alafenamide** (TAF)<br>**Only available as a component of fixed-dose combinations (by trade name and abbreviation):** | See fixed-dose combinations below. | See fixed-dose combinations below. | Metabolized by cathepsin A; P-glycoprotein substrate<br>Not recommended in patients with CrCl < 30 mL/min (see Appendix B, Table 7). | 0.5 hours/150–180 hours | • Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy; less likely than from TDF<br>• Osteomalacia, decrease in bone mineral density; lesser effect than from TDF<br>• Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TAF.<br>• Diarrhea, nausea, headache |
| *Descovy* (TAF/FTC) | Descovy:<br>• (FTC 200 mg plus TAF 25 mg) tablet | Descovy:<br>• 1 tablet once daily | | | |
| *Genvoya* (TAF/EVG/c/FTC) | Genvoya:<br>• (TAF 10 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet | Genvoya:<br>• 1 tablet once daily with food | | | |
| *Odefsey* (TAF/RPV/FTC) | Odefsey:<br>• (TAF 25 mg plus RPV 25 mg plus FTC 200 mg) tablet | Odefsey:<br>• 1 tablet once daily with a meal | | | |



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**Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 6)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination | Serum/ Intracellular Half-Lives | Adverse Events[b] |
|---|---|---|---|---|---|
| **Tenofovir Disoproxil Fumarate** (TDF) *Viread*<br><br>**Also available as a component of fixed-dose combinations (by trade name and abbreviation):** | Viread:<br>• 150, 200, 250, and 300 mg tablets<br>• 40 mg/g oral powder | Viread:<br>• 300 mg once daily, *or*<br>• 7.5 level scoops once daily (dosing scoop dispensed with each prescription; 1 level scoop contains 1 g of oral powder).<br>• Take without regard to meals.<br><br>Mix oral powder with 2–4 ounces of a soft food that does not require chewing (e.g., applesauce, yogurt). **Do not mix oral powder with liquid.** | Renal excretion is primary route of elimination.<br><br>Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7). | 17 hours/ >60 hours | • Renal insufficiency, Fanconi syndrome, proximal renal tubulopathy<br>• Osteomalacia, decrease in bone mineral density<br>• Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF.<br>• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence |
| *Atripla* (TDF/EFV/FTC) | Atripla:<br>• (TDF 300 mg plus EFV 600 mg plus FTC 200 mg) tablet | Atripla:<br>• 1 tablet at or before bedtime<br>• Take on an empty stomach to reduce side effects. | | | |
| *Complera* (TDF/RPV/FTC) | Complera:<br>• (TDF 300 mg plus RPV 25 mg plus FTC 200 mg) tablet | Complera:<br>• 1 tablet once daily<br>• Take with a meal. | | | |
| *Stribild* (TDF/EVG/c/FTC) | Stribild:<br>• (TDF 300 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg) tablet | Stribild:<br>• 1 tablet once daily<br>• Take with food. | | | |
| *Truvada* (TDF/FTC) | Truvada:<br>• (TDF 300 mg plus FTC 200 mg) tablet | Truvada:<br>• 1 tablet once daily<br>• Take without regard to meals. | | | |



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**Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 6)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination | Serum/ Intracellular Half-Lives | Adverse Events[b] |
|---|---|---|---|---|---|
| **Zidovudine** (ZDV) *Retrovir*<br>**Note:** Generic available<br>**Also available as a component of fixed-dose combinations (by trade name and abbreviation):** | Retrovir:<br>• 100 mg capsule<br>• 300 mg tablet (only available as generic)<br>• 10 mg/mL intravenous solution<br>• 10 mg/mL oral solution | Retrovir:<br>• 300 mg BID, *or*<br>• 200 mg TID<br>• Take without regard to meals. | Metabolized to GAZT<br>Renal excretion of GAZT<br>Dosage adjustment in patients with renal insufficiency is recommended (see Appendix B, Table 7). | 1.1 hours/ 7 hours | • Bone marrow suppression: macrocytic anemia or neutropenia<br>• Nausea, vomiting, headache, insomnia, asthenia<br>• Nail pigmentation<br>• Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity)<br>• Hyperlipidemia<br>• Insulin resistance/diabetes mellitus<br>• Lipoatrophy<br>• Myopathy |
| *Combivir* (ZDV/3TC)<br>**Note:** Generic available | Combivir:<br>• (ZDV 300 mg plus 3TC 150 mg) tablet | Combivir:<br>• 1 tablet BID<br>• Take without regard to meals. | | | |
| *Trizivir* (ZDV/3TC/ABC)<br>**Note:** Generic available | Trizivir:<br>• (ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg) tablet | Trizivir:<br>• 1 tablet BID<br>• Take without regard to meals. | | | |

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; BID = twice daily; c, COBI = cobicistat; CrCl = creatinine clearance; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; GAZT = azidothymidine glucuronide; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; MI = myocardial infarction; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times a day; WHO = World Health Organization; ZDV = zidovudine



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**Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)**

**Note:** Delavirdine (DLV) is not included in this table. Please refer to the DLV Food and Drug Administration package insert for related information.

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathway | Serum Half-Life | Adverse Events[b] |
|---|---|---|---|---|---|
| **Efavirenz** (EFV) *Sustiva*<br>**Also available as a component of fixed-dose combination (by trade name and abbreviation):** | Sustiva:<br>• 50 and 200 mg capsules<br>• 600 mg tablet | Sustiva:<br>• 600 mg once daily, at or before bedtime<br>• Take on an empty stomach to reduce side effects. | Metabolized by CYPs 2B6 (primary), 3A4, and 2A6<br>CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor)<br>CYP2C9 and 2C19 inhibitor; 2B6 inducer | 40–55 hours | • Rash[c]<br>• Neuropsychiatric symptoms[d]<br>• Increased transaminase levels<br>• Hyperlipidemia<br>• False-positive results with some cannabinoid and benzodiazepine screening assays reported.<br>• Teratogenic in non-human primates and potentially teratogenic during the first trimester of pregnancy in humans |
| *Atripla* (EFV/TDF/FTC) | Atripla:<br>• (EFV 600 mg plus TDF 300 mg plus FTC 200 mg) tablet | Atripla:<br>• 1 tablet once daily, at or before bedtime | | | |
| **Etravirine** (ETR) *Intelence* | • 25, 100, and 200 mg tablets | • 200 mg BID<br>• Take following a meal. | CYP3A4, 2C9, and 2C19 substrate<br>3A4 inducer; 2C9 and 2C19 inhibitor | 41 hours | • Rash, including Stevens-Johnson syndrome[c]<br>• HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) have been reported.<br>• Nausea |
| **Nevirapine** (NVP) *Viramune or Viramine XR*<br>Generic available for 200 mg tablets and oral suspension | • 200 mg tablet<br>• 400 mg XR tablet<br>• 50 mg/5 mL oral suspension | • 200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID, or 400 mg (Viramune XR tablet) once daily<br>• Take without regard to meals.<br>• Repeat lead-in period if therapy is discontinued for >7 days.<br>• In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves but not longer than 28 days total. | CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces | 25–30 hours | • Rash, including Stevens-Johnson syndrome[c]<br>• Symptomatic hepatitis, including fatal hepatic necrosis, has been reported:<br>  • Rash reported in approximately 50% of cases.<br>  • Occurs at significantly higher frequency in ARV-naive female patients with pre-NVP CD4 counts >250 cells/$mm^3$ and in ARV-naive male patients with pre-NVP CD4 counts >400 cells/$mm^3$. NVP should not be initiated in these patients unless the benefit clearly outweighs the risk. |



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## Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)

**Note:** Delavirdine (DLV) is not included in this table. Please refer to the DLV Food and Drug Administration package insert for related information.

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathway | Serum/ Half-Life | Adverse Events[b] |
|---|---|---|---|---|---|
| **Rilpivirine** (RPV) *Edurant*<br>**Also available as a component of fixed-dose combinations (by trade name and abbreviation):** | Edurant:<br>• 25 mg tablet | Edurant:<br>• 25 mg once daily<br>• Take with a meal. | CYP3A4 substrate | 50 hours | • Rash[c]<br>• Depression, insomnia, headache<br>• Hepatotoxicity |
| *Complera* (RPV/TDF/FTC) | Complera:<br>• (RPV 25 mg plus TDF 300 mg plus FTC 200 mg) tablet | Complera:<br>• 1 tablet once daily<br>• Take with a meal. | | | |
| *Odefsey* (RPV/TAF/FTC) | Odefsey:<br>• (RPV 25 mg plus TAF 25 mg plus FTC 200 mg) tablet | Odefsey:<br>• 1 tablet once daily<br>• Take with a meal. | | | |

[a] For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

[c] Rare cases of Stevens-Johnson syndrome have been reported with most NNRTIs; the highest incidence of rash was seen with NVP.

[d] Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, depression, suicidality (suicide, suicide attempt or ideation), confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2 to 4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.

**Key to Abbreviations:** ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DLV = delavirdine; EFV = efavirenz; ETR = etravirine; FDA = Food and Drug Administration; FTC = emtricitabine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; XR = extended release



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**Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 1 of 4)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathway | Serum Half-Life | Storage | Adverse Events[b] |
|---|---|---|---|---|---|---|
| **Atazanavir** (ATV) *Reyataz*<br>**Also available as a component of fixed-dose combination (by trade name and abbreviation):** | Reyataz:<br>• 100, 150, 200, and 300 mg capsules<br>• 50 mg single packet oral powder | In ARV-Naive Patients:<br>• (ATV 300 mg plus RTV 100 mg) once daily; *or*<br>• ATV 400 mg once daily<br>With TDF or in ARV-Experienced Patients:<br>• (ATV 300 mg plus RTV 100 mg) once daily<br>With EFV in ARV-Naive Patients:<br>• (ATV 400 mg plus RTV 100 mg) once daily<br>Take with food.<br>For recommendations on dosing with H2 antagonists and PPIs, refer to Table 19a. | CYP3A4 inhibitor and substrate; weak CYP2C8 inhibitor; UGT1A1 inhibitor<br>Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7). | 7 hours | Room temperature (up to 25° C or 77° F) | • Indirect hyperbilirubinemia<br>• PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation.<br>• Hyperglycemia<br>• Fat maldistribution<br>• Cholelithiasis<br>• Nephrolithiasis<br>• Renal insufficiency<br>• Serum transaminase elevations<br>• Hyperlipidemia (especially with RTV boosting)<br>• Skin rash<br>• Increase in serum creatinine (with COBI) |
| *Evotaz* (ATV/c) | Evotaz:<br>• (ATV 300 mg plus COBI 150 mg) tablet | Evotaz:<br>• 1 tablet once daily<br>• Take with food.<br>With TDF:<br>• **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl). | ATV: as above<br>COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor | | | |
| **Darunavir** (DRV) *Prezista*<br>**Also available as a component of fixed-dose combination (by trade name and abbreviation):** | • 75, 150, 600, and 800 mg tablets<br>• 100 mg/mL oral suspension | In ARV-Naive Patients or ARV-Experienced Patients with No DRV Mutations:<br>• (DRV 800 mg plus RTV 100 mg) once daily<br>In ARV-Experienced Patients with One or More DRV Resistance Mutations:<br>• (DRV 600 mg plus RTV 100 mg) BID<br>Unboosted DRV **is not recommended**.<br>Take with food. | CYP3A4 inhibitor and substrate<br>CYP2C9 inducer | 15 hours (when combined with RTV) | Room temperature (up to 25° C or 77° F) | • Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythrema multiforme have been reported.<br>• Hepatotoxicity<br>• Diarrhea, nausea<br>• Headache<br>• Hyperlipidemia<br>• Serum transaminase elevation<br>• Hyperglycemia<br>• Fat maldistribution<br>• Increase in serum creatinine (with COBI) |
| *Prezcobix* (DRV/c) | Prezcobix:<br>• (DRV 800 mg plus COBI 150 mg) tablet | Prezcobix:<br>• 1 tablet once daily<br>• Take with food.<br>**Not recommended** for patients with one or more DRV resistance-associated mutations.<br>With TDF:<br>• **Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl). | DRV: As above<br>COBI: substrate of CYP3A, CYP2D6 (minor); CYP3A inhibitor | | | |



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**Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 2 of 4)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathway | Serum Half-Life | Storage | Adverse Events[b] |
|---|---|---|---|---|---|---|
| **Fosamprenavir** (FPV) *Lexiva* (a prodrug of APV) | • 700 mg tablet<br>• 50 mg/mL oral suspension | In ARV-Naive Patients:<br>• FPV 1400 mg BID, *or*<br>• (FPV 1400 mg plus RTV 100–200 mg) once daily, *or*<br>• (FPV 700 mg plus RTV 100 mg) BID<br>In PI-Experienced Patients (**Once-Daily Dosing Not Recommended**):<br>• (FPV 700 mg plus RTV 100 mg) BID<br>With EFV:<br>• (FPV 700 mg plus RTV 100 mg) BID, *or*<br>• (FPV 1400 mg plus RTV 300 mg) once daily<br>*Tablet:*<br>• Without RTV tablet: Take without regard to meals.<br>• With RTV tablet: Take with meals.<br>*Oral Suspension:*<br>• Take without food. | APV is a CYP3A4 substrate, inhibitor, and inducer.<br>Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7). | 7.7 hours (APV) | Room temperature (up to 25º C or 77º F) | • Skin rash (12% to 19%): FPV has a sulfonamide moiety.<br>• Diarrhea, nausea, vomiting<br>• Headache<br>• Hyperlipidemia<br>• Serum transaminase elevation<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• Nephrolithiasis |
| **Indinavir** (IDV) *Crixivan* | • 100, 200, and 400 mg capsules | • 800 mg every 8 hours<br>• Take 1 hour before or 2 hours after meals; may take with skim milk or a low-fat meal.<br>With RTV:<br>• (IDV 800 mg plus RTV 100–200 mg) BID<br>• Take without regard to meals. | CYP3A4 inhibitor and substrate<br>Dosage adjustment in patients with hepatic insufficiency is recommended (see Appendix B, Table 7). | 1.5–2 hours | Room temperature (15º to 30º C or 59º to 86º F)<br>Protect from moisture. | • Nephrolithiasis<br>• GI intolerance, nausea<br>• Hepatitis<br>• Indirect hyperbilirubinemia<br>• Hyperlipidemia<br>• Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia |



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**Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 3 of 4)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathway | Serum Half-Life | Storage | Adverse Events[b] |
|---|---|---|---|---|---|---|
| **Lopinavir/ Ritonavir** (LPV/r) *Kaletra* | Tablets:<br>• (LPV 200 mg plus RTV 50 mg), *or*<br>• (LPV 100 mg plus RTV 25 mg)<br>Oral Solution:<br>• Each 5 mL contains (LPV 400 mg plus RTV 100 mg).<br>• Oral solution contains 42% alcohol. | • (LPV 400 mg plus RTV 100 mg) BID, *or*<br>• (LPV 800 mg plus RTV 200 mg) once daily<br>Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital.<br>With EFV or NVP (PI-Naive or PI-Experienced Patients):<br>• LPV/r 500 mg/125 mg tablets BID (use a combination of 2 LPV/r 200 mg/50 mg tablets plus 1 LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg), *or*<br>• LPV/r 520 mg/130 mg oral solution BID<br>*Tablet:*<br>• Take without regard to meals.<br>*Oral Solution:*<br>• Take with food. | CYP3A4 inhibitor and substrate | 5–6 hours | Oral tablet is stable at room temperature.<br>Oral solution is stable at 2° to 8° C (36° to 46° F) until date on label and is stable for up to 2 months when stored at room temperature (up to 25° C or 77° F). | • GI intolerance, nausea, vomiting, diarrhea<br>• Pancreatitis<br>• Asthenia<br>• Hyperlipidemia (especially hypertriglyceridemia)<br>• Serum transaminase elevation<br>• Hyperglycemia<br>• Insulin resistance/diabetes mellitus<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• PR interval prolongation<br>• QT interval prolongation and torsades de pointes have been reported; however, causality could not be established. |
| **Nelfinavir** (NFV) *Viracept* | • 250 and 625 mg tablets<br>• 50 mg/g oral powder | • 1250 mg BID, *or*<br>• 750 mg TID<br>Dissolve tablets in a small amount of water, mix admixture well, and consume immediately.<br>Take with food. | CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP3A4 inhibitor | 3.5–5 hours | Room temperature (15° to 30° C or 59° to 86° F) | • Diarrhea<br>• Hyperlipidemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• Serum transaminase elevation |
| **Ritonavir** (RTV) *Norvir*<br>**Also available as a component of fixed-dose combination (see Lopinavir/ Ritonavir)** | • 100 mg tablet<br>• 100 mg soft gel capsule<br>• 80 mg/mL oral solution<br>Oral solution contains 43% alcohol. | As Pharmacokinetic Booster (or Enhancer) for Other PIs:<br>• 100–400 mg per day in 1 or 2 divided doses (refer to other PIs for specific dosing recommendations).<br>*Tablet:*<br>• Take with food.<br>*Capsule and Oral Solution:*<br>• To improve tolerability, take with food if possible. | CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor; Inducer of CYPs 1A2, 2C8, 2C9, and 2C19 and UGT1A1 | 3–5 hours | Tablets do not require refrigeration.<br>Refrigerate capsules.<br>Capsules can be left at room temperature (up to 25° C or 77° F) for up to 30 days.<br>**Oral solution should not be refrigerated.** | • GI intolerance, nausea, vomiting, diarrhea<br>• Paresthesia (circumoral and extremities)<br>• Hyperlipidemia (especially hypertriglyceridemia)<br>• Hepatitis<br>• Asthenia<br>• Taste perversion<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia |



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**Appendix B, Table 3. Characteristics of Protease Inhibitors (Last updated September 9, 2016; last reviewed April 8, 2015) (page 4 of 4)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathway | Serum Half-Life | Storage | Adverse Events[b] |
|---|---|---|---|---|---|---|
| **Saquinavir** (SQV) *Invirase* | • 500 mg tablet<br>• 200 mg capsule | • (SQV 1000 mg plus RTV 100 mg) BID<br>• Unboosted SQV **is not recommended**.<br>• Take with meals or within 2 hours after a meal. | CYP3A4 substrate | 1–2 hours | Room temperature (15º to 30º C or 59º to 86º F) | • GI intolerance, nausea, and diarrhea<br>• Headache<br>• Serum transaminase elevation<br>• Hyperlipidemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• PR interval prolongation<br>• QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV. |
| **Tipranavir** (TPV) *Aptivus* | • 250 mg capsule<br>• 100 mg/mL oral solution | • (TPV 500 mg plus RTV 200 mg) BID<br>Unboosted TPV **is not recommended**.<br>With RTV Tablets:<br>• Take with meals.<br>With RTV Capsules or Solution:<br>• Take without regard to meals. | CYP P450 3A4 inducer and substrate<br>CYP2D6 inhibitor; CYP3A4, 1A2, and 2C19 inducer<br>Net effect when combined with RTV (CYP3A4, 2D6 inhibitor) | 6 hours after single dose of TPV/r | Refrigerate capsules.<br>Capsules can be stored at room temperature (25º C or 77º F) for up to 60 days.<br>**Oral solution should not be refrigerated or frozen** and should be used within 60 days after bottle is opened. | • Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor patients closely, especially those with underlying liver diseases.<br>• Skin rash (3% to 21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy.<br>• Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, and the use of anti-coagulant or anti-platelet agents (including vitamin E).<br>• Hyperlipidemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia |

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

**Key to Acronyms:** APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; AV = atrioventricular; BID = twice daily; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV = lopinavir; LPV/r = lopinavir/ritonavir; msec = millisecond; NFV = nelfinavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TID = three times a day; TPV = tipranavir



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**Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 2)**

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathways | Serum Half-Life | Adverse Events[b] |
|---|---|---|---|---|---|
| **Dolutegravir** (DTG) *Tivicay*<br>**Also available as a component of fixed-dose combination (by trade name and abbreviation):** | • 50 mg tablet | ARV-Naive or ARV-Experienced, INSTI-Naive Patients:<br>• 50 mg once daily<br>ARV-Naive or ARV-Experienced, INSTI-Naive Patients when Co-Administered with EFV, FPV/r, TPV/r, or Rifampin:<br>• 50 mg BID<br>INSTI-Experienced Patients with Certain INSTI Mutations (See Product Label) or with Clinically Suspected INSTI Resistance:<br>• 50 mg BID<br>Take without regard to meals. | UGT1A1 mediated glucuronidation<br>Minor contribution from CYP3A4 | ~14 hours | • HSRs, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported.<br>• Insomnia<br>• Headache<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions) |
| *Triumeq* (DTG/ABC/3TC) | Triumeq:<br>• (DTG 50 mg plus ABC 600 mg plus 3TC 300 mg) tablet | Triumeq:<br>• Take 1 tablet daily without regard to meals. | | | |
| **Elvitegravir** (EVG) *Vitekta*<br>**Also available as a component of fixed-dose combinations (by trade name and abbreviation):** | • 85 and 150 mg tablets | With Once Daily ATV/r or BID LPV/r:<br>• 85 mg once daily with food<br>With BID DRV/r, FPV/r, or TPV/r:<br>• 150 mg once daily with food<br>Unboosted EVG **is not recommended**. | CYP3A, UGT1A1/3 substrate | ~9 hours | • Nausea<br>• Diarrhea<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions) |
| *Genvoya* (EVG/c/FTC/TAF) | Genvoya:<br>• (EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg) tablet | Genvoya:<br>• 1 tablet once daily with food<br>**Not recommended** for patients with CrCl <30 mL/min (see Appendix B, Table 7 for the equation for calculating CrCl).<br>**Not recommended for use with other ARV drugs.** | EVG: As above<br>COBI: CYP3A, CYP2D6 (minor); CYP3A inhibitor | ~13 hours | |
| *Stribild* (EVG/c/FTC/TDF) | Stribild:<br>• (EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg) tablet | Stribild:<br>• 1 tablet once daily with food<br>**Not recommended** for patients with baseline CrCl <70 mL/min (see Appendix B Table 7 for the equation for calculating CrCl).<br>**Not recommended for use with other ARV drugs.** | | ~13 hours | |



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## Appendix B, Table 4. Characteristics of Integrase Inhibitors (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 2)

| Generic Name (Abbreviation) *Trade Name* | Formulations | Dosing Recommendations[a] | Elimination/ Metabolic Pathways | Serum Half-Life | Adverse Events[b] |
|---|---|---|---|---|---|
| **Raltegravir** (RAL) *Isentress* | • 400 mg tablet<br>• 25 and 100 mg chewable tablets<br>• 100 mg single packet for oral suspension | • 400 mg BID<br>With Rifampin:<br>• 800 mg BID<br>Take without regard to meals. | UGT1A1-mediated glucuronidation | ~9 hours | • Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis<br>• Nausea<br>• Headache<br>• Diarrhea<br>• Pyrexia<br>• CPK elevation, muscle weakness, and rhabdomyolysis<br>• Insomnia<br>• Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions) |

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BID = twice daily; c, COBI = cobicistat; CPK = creatine phosphokinase; CrCl = creatinine clearance; CYP = cytochrome P; DRV/r = darunavir/ritonavir; DTG = dolutegravirEFV = efavirenz; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HBV = hepatitis B virus; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumerate; TPV/r = tipranavir/ritonavir; UGT = uridine diphosphate gluconyltransferase

## Appendix B, Table 5. Characteristics of Fusion Inhibitor (Last updated January 29, 2008; last reviewed April 8, 2015)

| Generic Name (Abbreviation) *Trade Name* | Formulation | Dosing Recommendation | Serum Half-Life | Elimination | Storage | Adverse Events[a] |
|---|---|---|---|---|---|---|
| **Enfuvirtide** (T20) *Fuzeon* | • Injectable; supplied as lyophilized powder<br>• Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL. | • 90 mg (1 mL) subcutaneously BID | 3.8 hours | Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool | Store at room temperature (up to 25° C or 77° F). Re-constituted solution should be refrigerated at 2° to 8° C (36° to 46° F) and used within 24 hours. | • Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients<br>• Increased incidence of bacterial pneumonia<br>• HSR (<1% of patients): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Re-challenge is not recommended. |

[a] Also see Table 14.

**Key to Abbreviations:** BID = twice daily; HSR = hypersensitivity reaction; T20 = enfuvirtide



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**Appendix B, Table 6. Characteristics of CCR5 Antagonist (Last updated March 27, 2012; last reviewed April 8, 2015)**

| Generic Name (Abbreviation)/ *Trade Name* | Formulation | Dosing Recommendations[a] | Serum Half-Life | Elimination/ Metabolic Pathway | Adverse Events[b] |
|---|---|---|---|---|---|
| **Maraviroc** (MVC) *Selzentry* | • 150 and 300 mg tablets | • **150 mg BID** when given with drugs that are strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r)<br>• **300 mg BID** when given with NRTIs, T20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers<br>• **600 mg BID** when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor)<br>• Take without regard to meals. | 14–18 hours | CYP3A4 substrate | • Abdominal pain<br>• Cough<br>• Dizziness<br>• Musculoskeletal symptoms<br>• Pyrexia<br>• Rash<br>• Upper respiratory tract infections<br>• Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions<br>• Orthostatic hypotension, especially in patients with severe renal insufficiency |

[a] For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.

[b] Also see Table 14.

**Key to Abbreviations:** BID = twice daily; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T20 = enfuvirtide; TPV/r = tipranavir/ritonavir



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## Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 1 of 6)

See the reference section at the end of this table for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

<table>
<tr><th>ARVs<br>Generic Name<br>(Abbreviation)<br>Trade Name</th><th>Usual Daily Dose[a]</th><th>Dosing in Renal Insufficiency[b]</th><th>Dosing in Hepatic Impairment</th></tr>
<tr><td colspan="4">NRTIs<br>Stribild should not be initiated in patients with CrCl <70 mL/min. Use of the following fixed-dose combinations is not recommended in patients with CrCl <50 mL/min: Atripla, Combivir, Complera, Epzicom, Stribild, Triumeq, or Trizivir. Use of Truvada is not recommended in patients with CrCl <30 mL/min.</td></tr>
<tr><td>Abacavir<br>(ABC)<br>Ziagen</td><td>• 300 mg PO BID</td><td>No dosage adjustment necessary</td><td>Child-Pugh Class A:<br>• 200 mg PO BID (use oral solution)<br>Child-Pugh Class B or C:<br>• Contraindicated</td></tr>
<tr><td>Didanosine EC<br>(ddI)<br>Videx EC</td><td>Body Weight ≥60 kg:<br>• 400 mg PO once daily<br>Body Weight <60 kg:<br>• 250 mg PO once daily</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>125 mg</td></tr><tr><td>10–29</td><td>125 mg</td><td>125 mg</td></tr><tr><td><10, HD[c], CAPD</td><td>125 mg</td><td>75 mg oral solution</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Didanosine Oral Solution<br>(ddI)<br>Videx</td><td>Body Weight ≥60 kg:<br>• 200 mg PO BID, or<br>• 400 mg PO once daily<br>Body Weight <60 kg:<br>• 250 mg PO once daily, or<br>• 125 mg PO BID</td><td><table><tr><th colspan="3">Dose (Once Daily)</th></tr><tr><th>CrCl (mL/min)</th><th>≥60 kg</th><th><60 kg</th></tr><tr><td>30–59</td><td>200 mg</td><td>150 mg</td></tr><tr><td>10–29</td><td>150 mg</td><td>100 mg</td></tr><tr><td><10, HD[c], CAPD</td><td>100 mg</td><td>75 mg</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
<tr><td>Emtricitabine<br>(FTC)<br>Emtriva</td><td>• 200 mg oral capsule once daily, or<br>• 240 mg (24 mL) oral solution once daily</td><td><table><tr><th colspan="3">Dose</th></tr><tr><th>CrCl (mL/min)</th><th>Capsule</th><th>Solution</th></tr><tr><td>30–49</td><td>200 mg q48h</td><td>120 mg q24h</td></tr><tr><td>15–29</td><td>200 mg q72h</td><td>80 mg q24h</td></tr><tr><td><15 or on HD[c]</td><td>200 mg q96h</td><td>60 mg q24h</td></tr></table></td><td>No dosage recommendation</td></tr>
<tr><td>Lamivudine<br>(3TC)<br>Epivir</td><td>• 300 mg PO once daily, or<br>• 150 mg PO BID</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>30–49</td><td>150 mg q24h</td></tr><tr><td>15–29</td><td>1 x 150 mg, then 100 mg q24h</td></tr><tr><td>5–14</td><td>1 x 150 mg, then 50 mg q24h</td></tr><tr><td><5 or on HD[c]</td><td>1 x 50 mg, then 25 mg q24h</td></tr></table></td><td>No dosage adjustment necessary</td></tr>
</table>



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**Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 2 of 6)**

| ARVs Generic Name (Abbreviation) *Trade Name* | Usual Daily Dose[a] | Dosing in Renal Insufficiency[b] | Dosing in Hepatic Impairment |
|---|---|---|---|
| **NRTIs**, continued | | | |
| **Stavudine** (d4T) *Zerit* | Body Weight ≥60 kg:<br>• 40 mg PO BID<br>Body Weight <60 kg:<br>• 30 mg PO BID | **Dose**<br>**CrCl (mL/min)** / **≥60 kg** / **<60 kg**<br>26–50 / 20 mg q12h / 15 mg q12h<br>10–25 or on HD[c] / 20 mg q24h / 15 mg q24h | No dosage recommendation |
| **Tenofovir Alafenamide/ Emtricitabine** (TAF/FTC) *Descovy* | TAF only available as a component of fixed-dose combinations (i.e., *Descovy*, *Genvoya*, and *Odefsey*)<br>• TAF 10 mg PO daily with EVG/c (*Genvoya*), *or*<br>• TAF 25 mg PO daily in other FDCs | **CrCl (mL/min)** / **Dose**<br><30 or on HD[c] / Not recommended | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• No dosage recommendation |
| **Tenofovir Disoproxil Fumarate** (TDF) *Viread* | • 300 mg PO once daily | **CrCl (mL/min)** / **Dose**<br>30–49 / 300 mg q48h<br>10–29 / 300 mg twice weekly (every 72–96 hours)<br><10 and not on HD / No recommendation<br>On HD[c] / 300 mg q7d | No dosage adjustment necessary |
| **Tenofovir Disoproxil Fumarate/ Emtricitabine** (TDF/FTC) *Truvada* | • 1 tablet PO once daily | **CrCl (mL/min)** / **Dose**<br>30–49 / 1 tablet q48h<br><30 or on HD / Not recommended | No dosage recommendation |
| **Zidovudine** (AZT, ZDV) *Retrovir* | • 300 mg PO BID | **CrCl (mL/min)** / **Dose**<br><15 or on HD[c] / 100 mg TID or 300 mg once daily | No dosage recommendation |
| **NNRTIs** | | | |
| **Delavirdine** (DLV) *Rescriptor* | • 400 mg PO TID | No dosage adjustment necessary | No dosage recommendation; use with caution in patients with hepatic impairment. |
| **Efavirenz** (EFV) *Sustiva* | • 600 mg PO once daily, at or before bedtime | No dosage adjustment necessary | No dosage recommendation; use with caution in patients with hepatic impairment. |
| **Efavirenz/ Tenofovir Disoproxil Fumarate/ Emtricitabine** (EFV/TDF/FTC) *Atripla* | • 1 tablet PO once daily | Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level. | |



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**Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 3 of 6)**

| ARVs<br>Generic Name<br>(Abbreviation)<br>*Trade Name* | Usual Daily Dose[a] | Dosing in Renal Insufficiency[b] | Dosing in Hepatic Impairment |
|---|---|---|---|
| **NNRTIs**, continued | | | |
| **Etravirine**<br>(ETR)<br>*Intelence* | • 200 mg PO BID | No dosage adjustment necessary | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• No dosage recommendation |
| **Nevirapine**<br>(NVP)<br>*Viramune*<br>or<br>*Viramune XR* | • 200 mg PO BID, *or*<br>• 400 mg PO once daily (using Viramune XR formulation) | Patients on HD:<br>• Limited data; no dosage recommendation | Child-Pugh Class A:<br>• No dosage adjustment<br>Child-Pugh Class B or C:<br>• Contraindicated |
| **Rilpivirine**<br>(RPV)<br>*Edurant* | • 25 mg PO once daily | No dosage adjustment necessary | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• No dosage recommendation |
| **Rilpivirine/Tenofovir Alafenamide/ Emtricitabine**<br>(RPV/TAF/FTC)<br>*Odefsey* | • 1 tablet PO once daily | Not recommended for use in patients with CrCl <30 mL/min | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• No dosage recommendation |
| **Rilpivirine/Tenofovir Disoproxil Fumarate/ Emtricitabine**<br>(RPV/TDF/FTC)<br>*Complera* | • 1 tablet PO once daily | Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level. | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• No dosage recommendation |
| **PIs** | | | |
| **Atazanavir**<br>(ATV)<br>*Reyataz* | • 400 mg PO once daily, *or*<br>• (ATV 300 mg plus RTV 100 mg) PO once daily | No dosage adjustment for patients with renal dysfunction who do not require HD.<br>ARV-Naive Patients on HD:<br>• (ATV 300 mg plus RTV 100 mg) once daily<br>ARV-Experienced Patients on HD:<br>• ATV or ATV/r not recommended | Child-Pugh Class B:<br>• 300 mg once daily<br>Child-Pugh Class C:<br>• Not recommended<br>RTV boosting **is not recommended** in patients with hepatic impairment. |
| **Atazanavir/ Cobicistat**<br>(ATV/c)<br>*Evotaz* | • 1 tablet PO once daily | If Used with TDF:<br>• Not recommended for use in patients with CrCl <70 mL/min | Not recommended in patients with hepatic impairment |



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**Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 4 of 6)**

| ARVs<br>Generic Name<br>(Abbreviation)<br>*Trade Name* | Usual Daily Dose[a] | Dosing in Renal Insufficiency[b] | Dosing in Hepatic Impairment |
|---|---|---|---|
| **PIs**, continued | | | |
| **Darunavir**<br>(DRV)<br>*Prezista* | ARV-Naive Patients and ARV-Experienced Patients with No DRV Resistance Mutations:<br>• (DRV 800 mg plus RTV 100 mg) PO once daily<br>ARV-Experienced Patients with at Least One DRV Resistance Mutation:<br>• (DRV 600 mg plus RTV 100 mg) PO BID | No dosage adjustment necessary | Mild-to-Moderate Hepatic Impairment:<br>• No dosage adjustment<br>Severe Hepatic Impairment:<br>• Not recommended |
| **Darunavir/ Cobicistat**<br>(DRV/c)<br>*Prezcobix* | • 1 tablet PO once daily (only recommended for patients without DRV-associated resistance mutations) | If Used with TDF:<br>• Not recommended for use in patients with CrCl <70 mL/min | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• Not recommended |
| **Fosamprenavir**<br>(FPV)<br>*Lexiva* | • 1400 mg PO BID, *or*<br>• (FPV 1400 mg plus RTV 100–200 mg) PO once daily, *or*<br>• (FPV 700 mg plus RTV 100 mg) PO BID | No dosage adjustment necessary | PI-Naive Patients Only<br>*Child-Pugh Score 5–9:*<br>• 700 mg BID<br>*Child-Pugh Score 10–15:*<br>• 350 mg BID<br>PI-Naive or PI-Experienced Patients<br>*Child-Pugh Score 5–6:*<br>• (700 mg BID plus RTV 100 mg) once daily<br>*Child-Pugh Score 7–9:*<br>• (450 mg BID plus RTV 100 mg) once daily<br>*Child-Pugh Score 10–15:*<br>• (300 mg BID plus RTV 100 mg) once daily |
| **Indinavir**<br>(IDV)<br>*Crixivan* | • 800 mg PO q8h | No dosage adjustment necessary | Mild-to-Moderate Hepatic Insufficiency Because of Cirrhosis:<br>• 600 mg q8h |



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**Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 5 of 6)**

| ARVs<br>Generic Name<br>(Abbreviation)<br>*Trade Name* | Usual Daily Dose[a] | Dosing in Renal Insufficiency[b] | Dosing in Hepatic Impairment |
|---|---|---|---|
| **PIs**, continued | | | |
| **Lopinavir/Ritonavir**<br>(LPV/r)<br>*Kaletra* | • (LPV 400 mg plus RTV 100 mg) PO BID, *or*<br>• (LPV 800 mg plus RTV 200 mg) PO once daily | Avoid once-daily dosing in patients on HD. | No dosage recommendation; use with caution in patients with hepatic impairment. |
| **Nelfinavir**<br>(NFV)<br>*Viracept* | • 1250 mg PO BID | No dosage adjustment necessary | Mild Hepatic Impairment:<br>• No dosage adjustment<br>Moderate-to-Severe Hepatic Impairment:<br>• Do not use. |
| **Ritonavir**<br>(RTV)<br>*Norvir* | As a PI-Boosting Agent:<br>• 100–400 mg per day | No dosage adjustment necessary | Refer to recommendations for the primary PI. |
| **Saquinavir**<br>(SQV)<br>*Invirase* | • (SQV 1000 mg plus RTV 100 mg) PO BID | No dosage adjustment necessary | Mild-to-Moderate Hepatic Impairment:<br>• Use with caution.<br>Severe Hepatic Impairment:<br>• Contraindicated |
| **Tipranavir**<br>(TPV)<br>*Aptivus* | • (TPV 500 mg plus RTV 200 mg) PO BID | No dosage adjustment necessary | Child-Pugh Class A:<br>• Use with caution.<br>Child-Pugh Class B or C:<br>• Contraindicated |
| **INSTIs** | | | |
| **Dolutegravir**<br>(DTG)<br>*Tivicay* | • 50 mg once daily, *or*<br>• 50 mg BID | No dosage adjustment necessary | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• Not recommended |
| **Elvitegravir**<br>(EVG)<br>*Vitekta* | • 85 mg or 150 mg[a] once daily | No dosage adjustment necessary | Child-Pugh Class A or B:<br>• No dosage adjustment<br>Child-Pugh Class C:<br>• Not recommended |
| **Elvitegravir/ Cobicistat/Tenofovir Alafenamide/ Emtricitabine**<br>(EVG/c/TAF/FTC)<br>*Genvoya* | • 1 tablet once daily | Not recommended for use in patients with CrCl <30 mL/min | Mild-to-Moderate Hepatic Insufficiency:<br>• No dosage adjustment necessary<br>Severe Hepatic Insufficiency:<br>• Not recommended |



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**Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated July 14, 2016; last reviewed July 14, 2016) (page 6 of 6)**

| ARVs<br>Generic Name<br>(Abbreviation)<br>*Trade Name* | Usual Daily Dose[a] | Dosing in Renal Insufficiency[b] | Dosing in Hepatic Impairment |
|---|---|---|---|
| **INSTIs**, continued | | | |
| **Elvitegravir/ Cobicistat/ Tenofovir Disoproxil Fumarate/ Emtricitabine**<br>(EVG/c/TDF/FTC)<br>*Stribild* | • 1 tablet once daily | EVG/c/TDF/FTC **should not be initiated** in patients with CrCl <70 mL/min.<br>Discontinue EVG/c/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy. | Mild-to-Moderate Hepatic Insufficiency:<br>• No dosage adjustment necessary<br>Severe Hepatic Insufficiency:<br>• Not recommended |
| **Raltegravir**<br>(RAL)<br>*Isentress* | • 400 mg BID | No dosage adjustment necessary | Mild-to-Moderate Hepatic Insufficiency:<br>• No dosage adjustment necessary<br>Severe Hepatic Insufficiency:<br>• No recommendation |
| **Fusion Inhibitor** | | | |
| **Enfuvirtide**<br>(T20)<br>*Fuzeon* | • 90 mg subcutaneous BID | No dosage adjustment necessary | No dosage adjustment necessary |
| **CCR5 Antagonist** | | | |
| **Maraviroc**<br>(MVC)<br>*Selzentry* | • The recommended dose differs based on concomitant medications and potential for drug-drug interactions. See Appendix B, Table 6 for detailed dosing information. | CrCl <30 mL/min or on HD<br>*Without Potent CYP3A Inhibitors or Inducers:*<br>• 300 mg BID; reduce to 150 mg BID if postural hypotension occurs<br>*With Potent CYP3A Inducers or Inhibitors:*<br>• Not recommended | No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment. |

[a] Refer to Appendix B, Tables 1–6 for additional dosing information.

[b] Including with chronic ambulatory peritoneal dialysis and hemodialysis.

[c] On dialysis days, take dose after HD session.

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; AZT = zidovudine; BID = twice daily; c, COBI = cobicistat; CAPD = chronic ambulatory peritoneal dialysis; CrCl = creatinine clearance; CYP = cytochrome P; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DTG = dolutegravir; EC = enteric coated; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HD = hemodialysis; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PO = orally; q(n)d = every (n) days; q(n)h = every (n) hours; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TID = three times daily; TPV = tipranavir; XR = extended release; ZVD = zidovudine



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| Creatinine Clearance Calculation | |
|---|---|
| Male: $\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine})}$ | Female: $\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine})}$ |

| Child-Pugh Score | | | |
|---|---|---|---|
| **Component** | **Points Scored** | | |
| | **1** | **2** | **3** |
| **Encephalopathy**[a] | None | Grade 1–2 | Grade 3–4 |
| **Ascites** | None | Mild or controlled by diuretics | Moderate or refractory despite diuretics |
| **Albumin** | >3.5 g/dL | 2.8–3.5 g/dL | <2.8 g/dL |
| **Total bilirubin** or | <2 mg/dL (<34 µmol/L) | 2–3 mg/dL (34 µmol/L to 50 µmol/L) | >3 mg/dL (>50 µmol/L) |
| **Modified total bilirubin**[b] | <4 mg/dL | 4–7 mg/dL | >7 mg/dL |
| **Prothrombin time (seconds prolonged)** or | <4 | 4–6 | >6 |
| **International normalized ratio (INR)** | <1.7 | 1.7–2.3 | >2.3 |

[a] Encephalopathy Grades

**Grade 1:** Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

**Grade 2:** Drowsiness, disorientation, asterixis

**Grade 3:** Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

**Grade 4:** Coma, decerebrate posturing, flaccidity

[b] Modified total bilirubin used for patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

| Child-Pugh Classification | Total Child-Pugh Score[a] |
|---|---|
| Class A | 5–6 points |
| Class B | 7–9 points |
| Class C | >9 points |

[a] Sum of points for each component of the Child-Pugh Score



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